Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Balanced Crystalloids versus Saline in Critically Ill Adults

Supplementary Appendix

Contents

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SUPPLEMENTAL METHODS

A. Study Site Characteristics*

Medical ICU – The medical ICU at Vanderbilt University Medical Center is a 34-bed intensive care unit staffed by pulmonary and critical care medicine physicians, which specializes in the care of patients with sepsis and septic shock, acute respiratory failure, gastrointestinal bleeding, acute liver failure, drug toxicity or ingestion, and glucose disorders.

Neuro ICU – The neurological and neurosurgical ICU at Vanderbilt University Medical Center is a 22-bed intensive care unit staffed by critical care anesthesiologists, neurologists, and neurosurgeons, which specializes in the care of patients with brain tumors, strokes, intracranial hemorrhages, neuromuscular disorders, seizures, and other diseases of the brain and spinal cord.

Cardiac ICU – The cardiovascular ICU at Vanderbilt University Medical Center is a 27-bed intensive care unit staffed by critical care anesthesiologists, cardiologists, cardiac surgeons, thoracic surgeons, and vascular surgeons, which specializes in the care of patients with ST-segment elevation myocardial infarction (STEMI), advanced heart failure, cardiac surgeries, ventricular assist devices, extracorporeal membrane oxygenation, and heart transplant.

Trauma ICU – The Level I Trauma Center at Vanderbilt includes a 31-bed intensive and acute care unit staffed by trauma surgeons, which specializes in the care of patients with polytrauma, traumatic brain injury, and chest and abdominal trauma.

Surgical ICU – The surgical ICU at Vanderbilt University Medical Center is a 22-bed intensive care unit staffed by critical care anesthesiologists and surgeons, which specializes in the care of patients recovering from complex head and neck, thoracic, gastrointestinal, gynecological, urologic, orthopedic, oncologic, microvascular plastic, and transplant surgeries.

*For the 11,582 patients admitted to the five study ICUs in the year prior to the trial,[1,2] 68.9% of the intravenous isotonic crystalloid administered was 0.9% sodium chloride and 31.1% was balanced crystalloid. The ratio of the observed-to-expected in-hospital mortality (see *Definitions of Study Variables*) was 1.24 in the year prior to the study and 1.18 during the study.

B. Trial Registration

The Isotonic Solutions and Major Adverse Renal Events Trial (SMART) was written as a single trial protocol and approved by the Vanderbilt University institutional review board as a single trial. It was registered as two halves in clinicaltrials.gov because of the need to accommodate different enrollment start dates for different clusters (SMART-MED, NCT02444988, for the medical intensive care unit and SMART-SURG, NCT02547779, for the surgical intensive care units). The SMART trial was analyzed in accordance with a single pre-specified analysis plan published in *Trials* before the conclusion of enrollment.[1]

C. Informed Consent

Saline, lactated Ringer's solution, and Plasma-Lyte A® are all IV crystalloids currently used in the routine care of patients admitted to the ICUs at Vanderbilt University Medical Center. Currently, no high-quality data suggest that choice of crystalloid affects clinical outcomes among critically ill adults. During the SMART trial, each time a study crystalloid was ordered, the study confirmed that the treating clinician did not feel that a specific crystalloid was required for the safe treatment of that specific patient at that specific point in time (see *Study Treatments* section).

The trial was felt to pose minimal risk because (1) exposure to the study crystalloids occurred only for patients whose treating clinician had already decided to administer an IV isotonic crystalloid, (2) all of the crystalloid solutions examined were already used in routine practice in the study environment, (3) no definitive prior data suggested clinical outcomes were better with one crystalloid relative to the others, and (4) the study confirmed with every crystalloid order that the treating clinician did not feel any one crystalloid type was required for safe treatment of that specific patient at that specific time. Given the minimal risk, the focus of the study on crystalloid use at an ICU level, as well as the impracticability of consenting each patient admitted to each ICU prior to the first administration of crystalloid, a waiver of informed consent was granted by the Institutional Review Board at Vanderbilt University.

D. Definitions of Study Variables

Fluids

Intravenous fluid – For the SMART study, intravenous fluid was defined as the intravenous administration of any formulation of any volume at any rate of 0.9% sodium chloride, lactated Ringer's, Plasma-Lyte A®; 0.45% sodium chloride, 0.225% sodium chloride, dextrose in water, 20% or 5% human albumin solution, gelatins, dextrans, or hydroxyethyl starches. This included fluid given as a bolus, fluid given as maintenance infusions, fluid given as flushes, fluid given along with IV medications (e.g., "piggy-back", "carrier", "chaser", or "driver" fluid), fluid given through pressure-bag systems, fluid given as a part of thermodilution of pulmonary artery catheters, and fluid given to maintain the patency of peripheral venous access. This did not include medication diluents or oral fluids.

Isotonic crystalloid – For the SMART study, the term isotonic crystalloid was used to refer to any of 0.9% sodium chloride, lactated Ringer's, or Plasma-Lyte A®. Use of the term isotonic crystalloid was intended to distinguish these three fluids from colloid solutions and from significantly hypotonic (0.45% sodium chloride) or hypertonic (3% sodium chloride) crystalloid solutions, rather than to imply that the tonicities of 0.9% sodium chloride, lactated Ringer's, or Plasma-Lyte A® are precisely comparable to extracellular fluid.

Saline – For the SMART study, 0.9% sodium chloride was referred to as saline.

Balanced crystalloid – For the SMART study, lactated Ringer's or Plasma-Lyte A® were referred to as balanced crystalloids. Both lactated Ringer's solution and Plasma-Lyte A® contain less chloride than saline (Table S1), but other differences in composition lead some clinicians to prefer one over the other for particular patients. Allowing clinicians to select either lactated Ringer's solution or Plasma-Lyte A® when balanced crystalloids were assigned was intended to improve compliance and emulate how balanced crystalloids are used in practice.[1]

Relative contraindications to the assigned crystalloid – Accepted relative contraindications

for patients assigned to balanced crystalloid included hyperkalemia and brain injury. The severity of hyperkalemia and brain injury at which saline was used in favor of balanced crystalloids was determined by the treating clinician. The non-assigned crystalloid was also made available via the pharmacy if a formal statement was submitted that the attending physician felt the non-assigned crystalloid was required for the safe treatment of a specific patient. The decision to allow physicians to select hyperkalemia as a contraindication to balanced crystalloids was based on the perception of treating clinicians regarding the administration of fluid containing potassium to patients with elevated plasma potassium, despite data suggesting that the incidence of hyperkalemia may be greater with saline compared to balanced crystalloids among certain patient populations.[3,4] Similarly, despite small studies suggesting safety of Plasma-Lyte A® in traumatic brain injury,[5,6] concern that the relative hypotonicity of balanced crystalloids might increase intracranial pressure led us to systematically present clinicians with the option of administering 0.9% sodium chloride to patients with brain injury regardless of study group assignment.

Renal Function

Baseline creatinine – The value for baseline creatinine was determined in a hierarchical approach[1,7,8]. The lowest plasma creatinine between 12 months and 24 h prior to hospital admission was used when available. If no such creatinine value was available, the lowest plasma creatinine value between 24 h prior to hospital admission and the time of ICU admission was used. If no creatinine value was available between 12 months prior to hospital admission and the time of ICU admission, a baseline creatinine value was estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][9].

Acute kidney injury, stage II or greater – Stage II or greater acute kidney injury was defined according to Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria.[10] AKI present at enrollment (prevalent AKI) was defined as a first plasma creatinine measurement after enrollment at least 200% of the baseline value OR both (1) greater than 4.0 mg/dL and (2) increased at least 0.3 mg/dL from baseline. AKI developing after enrollment (incident AKI) was defined as: any creatinine value between enrollment and discharge or 30 days that was (1)

increased at least 0.3 mg/dL from a preceding post-enrollment value AND (2) at least 200% of the baseline value, at least 200% of a preceding post-enrollment value, or at least 4.0 mg/dL; or new receipt of RRT.

Chronic kidney disease stage III or greater – Chronic kidney disease stage III or greater was defined as a glomerular filtration rate less than 60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation[11] using the patient's baseline creatinine value.

Outcomes

Major Adverse Kidney Events within 30 days (MAKE30). The MAKE30 composite outcome[7,8,12,13] was considered to have occurred when patients met one or more of the following criteria in the 30 days after ICU admission and before hospital discharge: (1) in-hospital mortality, (2) receipt of new renal replacement therapy (RRT), or (3) persistent renal dysfunction (See Box 1). Patients who had received RRT prior to ICU admission were ineligible to meet the new RRT or persistent renal dysfunction criteria but remained eligible to meet criteria for in-hospital mortality.

In-hospital mortality – In-hospital mortality was defined as death from any cause prior to hospital discharge. For calculation of the primary outcome, in-hospital mortality was assessed 30 days after ICU admission (30-day in-hospital mortality). For secondary outcomes, in-hospital mortality was assessed before ICU discharge (in-ICU mortality) and 60 days after ICU admission (60-day in-hospital mortality).

Receipt of new renal replacement therapy – Receipt of new RRT was defined as receipt of any modality of RRT between ICU admission and the first of hospital discharge or 30 days among patients not known to have received RRT prior to ICU admission. The decision to initiate new RRT was made by treating clinicians. The study did not specify criteria defining when new RRT should be provided. At the study institution, the decision to initiate RRT for critically ill adults is made by a nephrology attending physician, in collaboration with the primary service caring for

the patient. Generally, this decision takes into account the patient's pre-illness comorbidities, acute diagnoses, severity of illness, potential indications for RRT, risk for complications from initiation of RRT, trajectory of critical illness, and prior wishes regarding supportive therapy.

Persistent renal dysfunction – Persistent renal dysfunction was defined as a final plasma creatinine value before hospital discharge (censored at 30 days after ICU admission) ≥ 200% of the baseline creatinine value[13].

Box 1. Definition of Major Adverse Kidney Events within 30 days (MAKE30)

Major Adverse Kidney Events within 30 days
One or more of the following criteria met in the 30 days after ICU admission: **In-hospital mortality** Death prior to hospital discharge **New receipt of RRT** Receipt of any modality of RRT prior to hospital discharge in a patient not known to have received RRT prior to ICU admission. **Persistent renal dysfunction** Final plasma creatinine value before hospital discharge ≥ 200% of the baseline plasma creatinine value in a patient not known to have received RRT prior to ICU admission.

ICU is intensive care unit; RRT is renal replacement therapy.

Background on the Major Adverse Kidney Events (MAKE) composite outcome – To address issues related to the design of clinical trials focused on the prevention and treatment of AKI, the National Institute of Diabetes and Digestive and Kidney Diseases sponsored a workshop titled "Clinical Trials in Acute Kidney Injury: Current Opportunities and Barriers" in December 2010 that brought together academic investigators, industry partners, and representatives from the National Institutes of Health and the Food and Drug Administration. One of the topics addressed by the workgroup was the optimal endpoint for a phase III or Phase IV randomized trial examining the early treatment of AKI. The workgroup recommended that:

"For an early intervention (e.g., after a small increase in SCr or positive result for a putative

biomarker), a composite endpoint of death, provision of dialysis (or reaching prespecified criteria at which dialysis would typically be instituted), or a sustained loss of kidney function at a discrete time point (e.g., 28 or 60 days) would be meaningful."[12]

The rationale given for use of a composite endpoint was:

"A composite endpoint is necessary because although each component is an important clinical endpoint, the event rate for each individually is likely to be too low to power a phase 3 clinical trial with a feasible sample size. Moreover, a therapeutic agent or strategy that enhances kidney function but results in an increased risk of death would not be desirable. Recent data demonstrate that AKI is associated with poor long-term outcomes. However, the full effect of nonrecovery or a sustained decline in kidney function (e.g., a 25%, 50%, or 100% rise in serum creatinine concentration over a given time interval) has not yet been completely defined."[14]

The separate report from the workgroup specifically addressing trials conducted in the ICU, among patients with sepsis, or among patients critically ill from trauma or surgery stated:

"Expanded composite endpoints that would be appropriate in phase 2 studies include death, the adjudicated need for acute dialysis, and doubling of baseline serum creatinine concentration (SCr)."[15]

Recent expert opinion on the selection of endpoints in clinical studies of AKI among critically ill adults has reinforced the potential value of the MAKE outcome for clinical trials involving the treatment of AKI:

"New onset or worsening of CKD, dialysis, and death represent hard clinical outcomes that are appropriate endpoints for AKI treatment trials…Using a composite endpoint increases the event rate for the assessment of therapies, includes a greater percentage of patients with a meaningful poor outcome, and prevents the constraint of competing risks associated with single outcomes."[16]

Shortly after publication of the recommendations of the NIDDK workgroup on clinical trials in AKI, an observational study of acute kidney injury biomarkers employed the MAKE composite outcome with the following definition:

"We defined major adverse kidney events (MAKE30) as the composite of death, use of renal replacement therapy, or persistence of renal dysfunction (defined by serum creatinine ≥200% of reference) at hospital discharge truncated at 30 days."[13]

We used the same definition in the design of the SMART trial (see Box 1 above). Three important considerations with this definition of the MAKE outcome are: timing of assessment (30 days); timing of censoring (hospital discharge); and definition of the persistent renal dysfunction component. Some authors have recommended extending the assessment of MAKE from 30 days to 90 days to reflect progression to chronic kidney disease rather than slowly resolving AKI, and including creatinine values obtained after hospital discharge.[17] Other authors have extended the assessment of MAKE for up to 6 years of follow up.[18] In preparation for the SMART trial, we explored the relationship between MAKE censored at the first of 30 days or hospital discharge and MAKE censored at 90 days, including post-discharge data.[7] Less than 0.5% of patients experienced new RRT between the first of 30 days or hospital discharge and 90 days. The most common cause of meeting MAKE90 criteria without having met MAKE30 criteria was a new or recurrent illness requiring hospitalization complicated by either death or new AKI. Given the aim of the SMART trial to evaluate the effect of IV crystalloid administration during acute illness on clinical outcomes, we felt that extending the assessment period from 30 to 90 days would risk increasing the influence of factors unrelated to crystalloid group assignment on the MAKE30 composite outcome. Additionally, data on death, new RRT, and persistent renal dysfunction between ICU admission and the first of 30 days or hospital discharge could be obtained through the electronic health record with no missing data, whereas data after hospital discharge was potentially susceptible to missing data and loss to follow up. Whether a final creatinine value ≥ 200% of the baseline creatinine value is the optimal definition for persistent renal dysfunction is unknown. We employed this threshold as it had been recommended by the NIDDK for AKI trials in the intensive care unit[15] and had been used in a prior study examining the incidence of MAKE30 among critically ill adults.[13]

ICU-free days – Intensive care unit-free days to day 28 (ICU-free days) was defined as the number of days from the time of the patient's physical transfer out of the ICU until day 28 after enrollment. Patients who died prior to day 28 after enrollment received a value of 0 for ICU-free days. Patients who were never transferred out of the ICU prior to day 28 after enrollment received a value of 0 for ICU-free days. Patients who were transferred out of the ICU, returned to the ICU, and were not subsequently transferred out of the ICU again before day 28 after enrollment received a value of 0 for ICU-free days. For patients who were transferred out of the ICU, were readmitted to the ICU, and were subsequently transferred out of the ICU again prior to day 28 after enrollment, ICU-free days were awarded based on the time of the final transfer out of the ICU prior to day 28 after enrollment.

Ventilator-free days – Ventilator-free days to day 28 (VFDs) were defined as the number of days from the time of initiating unassisted breathing (breathing without support of the mechanical ventilator) until day 28 after enrollment. Patients who died prior to day 28 after enrollment received a value of 0 for VFDs. Patients who never achieved unassisted breathing prior to day 28 after enrollment received a value of 0 for VFDs. Patients who achieved unassisted breathing, returned to assisted breathing, and did not again achieve unassisted breathing before day 28 after enrollment received a value of 0 for VFDs. For patients who achieved unassisted breathing, returned to assisted breathing, and subsequently achieved unassisted breathing again prior to day 28 after enrollment, VFDs were awarded based on the time of the final initiation of unassisted breathing prior to day 28 after enrollment. Survivors who never experienced assisted breathing received 28 VFDs.

Vasopressor-free days – Vasopressor-free days to day 28 were defined as the number of days from the time of vasopressor cessation until day 28 after enrollment. Patients who died prior to day 28 after enrollment received a value of 0 for vasopressor-free days. Patients who never ceased to receive vasopressors prior to day 28 after enrollment received a value of 0 for vasopressor-free days. Patients who achieved vasopressor cessation, returned to receiving vasopressors, and did not again achieve vasopressor cessation before day 28 after enrollment received a value of 0 for vasopressor-free days. For patients who achieved vasopressor

cessation, returned to receiving vasopressors, and subsequently achieved cessation of vasopressors again prior to day 28 after enrollment, vasopressor-free days were awarded based on the time of the final cessation of vasopressors prior to day 28 after enrollment. Survivors who never received vasopressors received 28 vasopressor-free days.

Renal replacement therapy-free days – Renal replacement therapy-free days to day 28 (RRT-free days) were defined as the number of days from the time of the final RRT treatment until day 28 after enrollment. Patients who died prior to day 28 after enrollment received a value of 0 for RRT-free days. Patients who continued to receive RRT through day 28 after enrollment received a value of 0 for RRT-free days. Patients who achieved RRT cessation, returned to receiving RRT, and did not again achieve RRT cessation before day 28 after enrollment received a value of 0 for RRT-free days. For patients who achieved RRT cessation, returned to receiving RRT, and subsequently achieved cessation of RRT again prior to day 28 after enrollment, RRT-free days were awarded based on the time of the final RRT treatment prior to day 28 after enrollment. Survivors who never received RRT were awarded 28 RRT-free days.

Enrollment

Enrollment occurred at the time of the patient's first ICU admission during a given hospitalization. Enrolled patients who were discharged from the hospital were eligible again if they were re-admitted to a participating ICU during a subsequent hospitalization. All study endpoints were assessed between enrollment and hospital discharge. For the primary analysis, the baseline characteristics, fluid receipt, and outcomes were compared between groups for each patient within a single hospitalization. A pre-specified secondary analysis included only the first hospitalization for each patient.

Group Assignment

Each month of the study, each participating ICU was assigned to use either saline or balanced crystalloids. The study group to which each patient was assigned (balanced crystalloid group vs saline group) was determined by the crystalloid assignment of the ICU at the time of the patient's first ICU admission during a given hospitalization. Each day, patients received the crystalloid to

which their ICU was assigned. Patients who remained in an ICU through a crossover (i.e., from one calendar month to another) may have received both types of crystalloid. Potential combinations of group assignment and crystalloid receipt are described in the following hypothetical clinical vignettes:

May 2nd 2016 – *a patient presenting to the Emergency Department (ED) with sepsis is admitted to the medical ICU for 7 days, transferred to the medical ward for 3 days, and then discharged home.* This patient would have been assigned to the balanced crystalloid group, as this was the crystalloid to which the medical ICU was assigned in May 2016 (see Supplemental Figure S1). If no relative contraindications to balanced crystalloid were present, the patient would have been treated with balanced crystalloids whenever an isotonic crystalloid was ordered in the ED and medical ICU. Choice of crystalloid on the medical ward would have been determined by treating clinicians.

July 14th 2016 – *a patient undergoes laminectomy in a neurosurgical operating room (OR), is admitted to the neurological ICU for 3 days, and is discharged to rehabilitation.* This patient would have been assigned to the saline group, as this was the crystalloid to which the neurological ICU was assigned in July 2016. The patient would have been treated with 0.9% sodium chloride whenever an isotonic crystalloid was ordered in the neurosurgical OR and neurological ICU.

October 31st 2016 – *a patient treated at an outside facility for ST-segment elevation myocardial infarction is transferred to the cardiac ICU for 4 days and then transferred to rehabilitation.* This patient would have been assigned to the balanced crystalloid group, as this was the crystalloid to which the cardiac ICU was assigned in October 2016. Crystalloid administered at the outside facility would not have been controlled by the study. Any isotonic crystalloid ordered in the cardiac ICU after November 1st 2016 at midnight would have been 0.9% sodium chloride, according to the assignment of the cardiac ICU for November 2016. In the pre-specified, intention-to-treat primary analysis, this patient would be analyzed in the balanced

crystalloid group. Any 0.9% sodium chloride the patient received during November would represent "contamination" with non-assigned crystalloid, even though it was introduced by the design of the trial (presented as the cumulative volume of isotonic crystalloid "After an ICU crossover in fluid assignment" in Table S5). This patient would have been excluded from the pre-specified secondary analyses excluding patients admitted within 7 days of a cross-over or excluding patients who experienced a cross-over (see Table S10).

January 20th 2017 – *a Level 1 trauma patient presenting to the ED with hemorrhagic shock is admitted to the trauma ICU and treated with blood transfusion but not isotonic crystalloid.* This patient would have been assigned to the balanced crystalloid group, as this was the crystalloid to which the Trauma ICU was assigned in January 2017. Even though this patient did not receive any isotonic crystalloid after ICU admission, the patient may have received the assigned crystalloid in the ED prior to ICU admission. This patient would have been included in the pre-specified, intention-to-treat primary analysis. This patient would have been excluded from the pre-specified modified intention-to-treat analysis limited to patients for whom ≥ 500 ml of isotonic crystalloid was ordered in the 72 hours after ICU admission (Table S10).

March 3rd 2017 – *a patient transferred to the surgical ICU after an otolaryngology procedure at an outside hospital is found to have an acute ischemic stroke, transferred to the neurological ICU for 6 days, and then discharged to rehabilitation.* This patient would have been assigned to the balanced crystalloid group, as this was the crystalloid to which the surgical ICU was assigned in March 2017. Crystalloid administered at the outside facility would not have been controlled by the study. Any isotonic crystalloid ordered after transfer to the neurological ICU would have been 0.9% sodium chloride, according to the assignment of the neurological ICU for March 2017. In the pre-specified, intention-to-treat primary analysis, this patient would be analyzed in the balanced crystalloid group. Any 0.9% sodium chloride the patient received in the neurological ICU would represent "contamination" with non-

assigned crystalloid, even though it was introduced by the design of the trial. This patient would have been excluded from the pre-specified secondary analyses excluding patients who were transferred between ICUs during the trial (see Table S10).

Although the cluster-crossover design introduced the potential for "contamination" with non-assigned crystalloid after an ICU crossover in crystalloid assignment, because the majority of crystalloid was ordered shortly after ICU admission (Figure 2), the volume of non-assigned crystalloid introduced as a result of an ICU crossover in fluid assignment was a median of 0 mL [IQR 0 – 0 mL] in both study groups (Table S5).

E. Electronic Health Record-based Data Collection

Electronically-extracted data – Structured data from the study institution's enterprise electronic health record (EHR) were exported daily to an Enterprise Data Warehouse (EDW), along with data from the patient registration, billing, and laboratory clinical information systems. Patient identifiers (medical record number and encounter number) and a timestamp for study enrollment (date and time of first ICU admission during the hospitalization) were used to extract the pre- and post-enrollment data elements below[7].

Collection of baseline creatinine – Using all inpatient, outpatient, and emergency department creatinine values from our institutional laboratory clinical information system (excluding point-of-care testing), we determined (1) the lowest plasma creatinine value between 12 months and 24 hours prior to hospital admission, (2) the lowest creatinine value between 24 hours prior to hospital admission and the time of ICU admission, and (3) an estimated baseline creatinine value using a previously-described three-variable formula [creatinine =0.74− 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)]. A baseline creatinine value for each patient was determined using the hierarchical approach described above[7].

Collection of demographic characteristics – Gender, age, race, height, weight, and body mass index were extracted from the MediPac patient registration system into the EDW.

Collection of admitting location – Admitting location was extracted from the MediPac patient registration system.

Collection of sepsis diagnosis – A diagnosis of sepsis or septic shock was determined according to the criteria outlined by the Centers for Medicare and Medicaid Services and the National Center for Health Statistics in the International Classification of Diseases, 10th Edition, Clinical Modification System (ICD-10-CM) Official Guidelines for Coding and Reporting[19] and the Hospital Inpatient Quality Reporting Program Measures ICD-10-CM DRAFT Code Sets[20]. Sepsis or septic shock was considered to be present if billing records for the hospitalization contained, in the first five billing codes, any of the following ICD-10-CM codes: A02.1, A22.7,

A26.7, A32.7, A40.0, A40.1, A40.3, A40.8, A40.9, A41.01, A41.02, A41.1, A41.2, A41.3, A41.4, A41.50, A41.51, A41.52, A41.53, A41.59, A41.81, A41.89, A41.9, A42.7, A54.86, B37.7, R65.20, R65.21; or any of the corresponding ICD-9-CM codes: 038.0, 038.1, 038.11, 038.12, 038.19, 038.2, 038.3, 038.4, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 995.91, 995.92. In the ICUs involved in this study, this approach has previously been demonstrated to correctly classify the presence or absence of sepsis in 92.8% of cases, when compared to the reference standard of physician chart review[21].

Collection of traumatic brain injury diagnosis – A diagnosis of traumatic brain injury was determined according to the proposed ICD-10-CM surveillance definition for traumatic brain injury outlined by the National Center for Health Statistics and the National Center for Injury Prevention and Control[22]. Traumatic brain injury was considered to be present if billing records for the hospitalization contained, in the first five billing codes, any of the following ICD-10-CM codes: S02.0, S02.1-, S02.8, S02.91, S04.02, S04.03-, S04.04-, S06-, S07.1.

Collection of severity of illness – Our institution participates in the Vizient Clinical Data Base and Resource Manager™ (formerly University HealthSystem Consortium), which provides an estimated expected mortality for each inpatient encounter based on coded data for age, gender, comorbidities present at the time of hospital admission, admission source, race, and principal diagnosis(www.vizientinc.com).[23–25] We have previously validated the performance of these expected mortality estimates for in-hospital mortality among critically ill adults at the study institution.[26] We retrieved these expected mortality estimates via our EDW for each patient in our cohort.

Intravenous fluid orders – We created a list of intravenous crystalloid fluids by manual review of all of fluid order types at our hospital. This list was used to extract fluid order data from the institutional EDW. We retrieved data by matching against medical record number and date of administration.

Laboratory values – We created a list of applicable laboratory studies by manual review of all laboratory types which matched the values of interest, and extracted laboratory values from our

Cerner laboratory system via our EDW.

Receipt of renal replacement therapy – RRT was identified electronically by the presence of any one of the following American Medical Association's Current Procedural Terminology (CPT) codes (3066 F, 4054 F, 4055 F, 90963, 90964, 90965, 90966, 90967, 90968, 90969, 90970, 90989, 90993, G0257, G8714, G8956, G9013, G9014, G9231, 90935, 90937, 90945, 90947, 90989, 90993, 90921, 90925, 90999) or International Classification of Disease, Clinical Modification (ICD) codes for ICD-9 (39.95, 54.98) and ICD-10 (5A1D00Z, 5A1D60Z, 3E1M39Z) in the patient registration system or billing system. In the study ICUs, this approach has previously been demonstrated to correctly classify the presence or absence of RRT receipt during an inpatient stay in 100% of cases.[7]

New receipt of renal replacement therapy – For all patients identified as receiving RRT during the study period, study personnel blinded to group assignment performed manual review of the pre-enrollment EHR to identify patients who had received RRT prior to enrollment, including at an outside facility. Patients who, on manual review, had not received RRT prior to enrollment and received RRT between enrollment and hospital discharge, censored at 30 days, were considered to have met the "new receipt of renal replacement therapy" component of the MAKE30 endpoint.[7]

Receipt of mechanical ventilation – Mechanical ventilation was determined by review of Medipac technical billing data. The number of calendar days with billing for mechanical ventilation was retrieved for each continuous period that each patient was admitted to an intensive care unit.

Receipt of vasopressors – Administration of vasopressors was determined by review of Medipac technical billing data. The number of calendar days with billing for vasopressors was retrieved for each continuous period that each patient was admitted to an intensive care unit.

In-hospital mortality – In-hospital mortality was determined by searching for a mortality-associated discharge disposition in our patient registration system after the date of enrollment.

Patients with a mortality-associated discharge disposition within 30 days of study enrollment were considered to have met the mortality component of the MAKE30 endpoint and those with a mortality-associated discharge disposition within 60 days of study enrollment were considered to have met criteria for the secondary endpoint of 60-day in-hospital mortality. In the study ICUs, this approach has been previously demonstrated to correctly classify the presence or absence of in-hospital mortality in 100% of cases[7].

F. Interim Analyses

An independent data and safety monitoring board (DSMB) oversaw the conduct of the trial and reviewed two interim analyses. The first interim analysis occurred 6 months after initiation of enrollment, examining patients enrolled between June 1, 2015 and November 30, 2015. The second interim analysis occurred halfway between the first interim analysis and the end of the trial, examining patients enrolled between June 1, 2015 and July 31, 2016. Both interim analyses used the same stopping criteria:

> *The stopping boundary for efficacy will be met if (1) the unadjusted difference in the incidence of the primary outcome (MAKE30) between study groups is greater than or equal to 2.6% with a P value less than 0.001 and (2) the P value is less than 0.001 for the difference between study groups in the incidence of either in-hospital mortality or receipt of new RRT. Because even small differences between groups would be clinically meaningful, and given the importance of determining with as much certainty as possible whether balanced crystalloids are superior to saline, a futility stopping boundary will not be employed. Use of the conservative Haybittle-Peto boundary (P < 0.001) will allow the final analysis to be performed using an unchanged level of significance (P = 0.05).*

After the second interim analysis, the DSMB recommended continuation of the trial to completion.

Use of the Haybittle-Peto boundary (P<0.001) for each interim analysis would allow the final analysis of the primary outcome to be performed using an unchanged level of significance (P=0.05). To use a more conservative approach, however, we have adjusted the critical P value for the primary endpoint analysis to 0.048 to take into account the interim analyses and ensure a family-wise Type I error rate of 0.05 for all tests of the primary endpoint.

G. Multivariable Modeling

The development of the models for the primary and secondary analyses have been described previously.[1] All binary outcomes were analyzed using a pre-specified generalized linear mixed-effects model specifying a binomial distribution for the response with logit link-function. Intensive care unit was included as the random intercept and group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury as fixed effects. ICU was included as a random effect to account for the correlation of patients within each ICU; the other covariates were felt to be clinically relevant predictors of the primary outcome.[1] All continuous outcomes were analyzed using a proportional odds model with cluster sandwich covariance estimator with intensive care unit as a cluster and the same pre-specified covariates. For the outcomes of new RRT receipt and duration of RRT, there were inadequate patients in the traumatic brain injury subgroup who experienced new RRT for appropriate fit of the model and this covariate was not included in the modeling of these two outcomes. For the primary analysis, both the marginal and conditional effects are reported. The marginal effect is the effect of study group averaged across the whole study population while the conditional effect is averaged within an ICU. For secondary analyses with ICU as a random effect, the conditional effect is reported. For the primary outcome of MAKE30, the observed intra-cluster correlation during the trial was 0.06, the intra-period correlation was <0.001, and the intra-cluster intra-period correlation was <0.001.

H. Effect modification ("subgroup") analyses

Using generalized linear mixed-effects modeling with a random effect for ICU, we examined the interaction between crystalloid assignment and the following pre-specified baseline variables with respect to the primary outcome of MAKE30 in the intention-to-treat population:

a. Source of admission to the ICU (*ED, operating room, transfer from another hospital, hospital ward, other*)

b. Study ICU (*medical, surgical, cardiac, neurological, trauma*)

c. Sepsis or septic shock (*yes, no*)

d. Traumatic brain injury (*yes, no*)

e. Receipt of mechanical ventilation (*yes, no*)

f. Receipt of vasopressors (*yes, no*)

g. Category of renal dysfunction at the time of enrollment (*no renal dysfunction, AKI, chronic kidney disease, end-stage renal disease receiving RRT*)

h. Predicted risk of in-hospital mortality (*continuous variable ranging from 0.0 to 1.0*)[27]

I. Handling of Missing Baseline Creatinine

For patients without a measured plasma creatinine between 12 months prior to hospital admission and enrollment, baseline creatinine value for the primary analysis was estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][9]. Multiple sensitivity analyses employed alternative approaches to estimating missing baseline creatinine values:

1) A 'complete cases' analysis was performed in which patients without a measured creatinine value between 12 months prior to hospital admission and enrollment were excluded.
2) Missing baseline plasma creatinine values were imputed by multivariable single imputation using the R function aregImpute in Hmisc package with 5 imputations. The imputation model included age, gender, race, group assignment, source of admission, primary diagnosis, receipt of mechanical ventilation, vasopressor receipt, prior hemodialysis, total fluids received in 30 days, UHC expected mortality, overall mortality, new RRT received, minimum creatinine value, maximum creatinine value, and final study creatinine value. Continuous variables were transformed via cubic splines with 3 to 5 knots.
3) Simple imputation was performed in which first creatinine value after enrollment was used as the baseline creatinine.
4) Simple imputation was performed in which the highest creatinine value between enrollment and 30 days was used as the baseline creatinine.
5) Simple imputation was performed in which the lowest creatinine value between enrollment and 30 days was used as the baseline creatinine.

J. Adverse Events

The prospectively collected primary and secondary outcomes (e.g., in-hospital mortality) and laboratory measures (e.g., hyperchloremia) were classified as study outcomes and not adverse events. One additional adverse event was reported. A patient with severe congestive heart failure and a left ventricular assist device was admitted with septic shock and required new continuous renal replacement therapy. The patient was in the group assigned to balanced crystalloid. The patient inadvertently received Plasma-Lyte A® as post-filter replacement fluid during continuous RRT for 8 hours instead of 0.9% sodium chloride, which was to be used for the performance of RRT regardless of group assignment. During the time in which Plasma-Lyte A® was use as post-filter replacement fluid instead of 0.9% sodium chloride, the patient was on continuous hemodynamic monitoring with no significant changes in heart rate, systolic blood pressure, or vasopressor requirement. Serial laboratory values measured during continuous RRT did not demonstrate new electrolyte or acid-base abnormalities. The patient experienced clinical improvement over the following 72 hours. The adverse event was reported to the DSMB and a plan was jointly formulated to prevent future use of fluids other than 0.9% sodium chloride for post-filter replacement during continuous RRT during the trial.

SUPPLEMENTAL TABLES

Table S1. Composition of the study fluids.

	Sodium	Potassium	Calcium	Magnesium	Chloride	Acetate	Lactate	Gluconate	Osmolarity
Plasma	135–145	4.5–5.0	2.2–2.6	0.8–1.0	94–111		1–2		275–295
0.9% saline	154				154				308
Lactated Ringer's	130	4.0	2.7		109		28		273
Plasma-Lyte A®	140	5.0		3.0	98	27		23	294

All values are in mEq/L except calculated osmolarity, which is in mOsm/L. 0.9% saline is "Sodium Chloride Injection, USP", lactated Ringer's is "lactated Ringer's Injection, USP", and Plasma-Lyte A® is "Multiple Electrolyte Injection, Type 1, USP", all from Baxter Healthcare Corporation in Deerfield, IL, USA.

Table S2. Elixhauser comorbidity index.

	Balanced	Saline
Comorbidity, No. (%)*	**(n = 7942)**	**(n = 7860)**
Congestive heart failure	1720 (21.7)	1690 (21.5)
Cardiac arrhythmias	2719 (34.2)	2598 (33.1)
Valvular disease	977 (12.3)	945 (12.0)
Peripheral vascular disorders	1006 (12.7)	1053 (13.4)
Pulmonary circulation disorders	814 (10.2)	850 (10.8)
Hypertension, uncomplicated	3350 (42.2)	3310 (42.1)
Hypertension, complicated	1396 (17.6)	1448 (18.4)
Paralysis	724 (9.1)	800 (10.2)
Other neurological disorders	2157 (27.2)	2106 (26.8)
Chronic pulmonary disease	1660 (20.9)	1664 (21.2)
Diabetes, uncomplicated	1137 (14.3)	1034 (13.2)
Diabetes, complicated	1366 (17.2)	1282 (16.3)
Hypothyroidism	1089 (13.7)	1016 (12.9)
Renal failure	1389 (17.5)	1409 (17.9)
Liver disease	894 (11.3)	909 (11.6)
Peptic ulcer disease excluding bleeding	135 (1.7)	134 (1.7)
Acquired immunodeficiency syndrome	56 (0.7)	65 (0.8)
Lymphoma	125 (1.6)	137 (1.7)
Metastatic cancer	425 (5.4)	444 (5.6)
Solid tumor without metastasis	721 (9.1)	659 (8.4)
Coagulopathy	1244 (15.7)	1274 (16.2)
Obesity	1322 (16.6)	1327 (16.9)
Weight loss	1321 (16.6)	1251 (15.9)
Fluid and electrolyte disorders	3906 (49.2)	3981 (50.6)
Blood loss anemia	90 (1.1)	107 (1.4)
Deficiency anemias	1400 (17.6)	1417 (18.0)
Alcohol abuse	709 (8.9)	772 (9.8)
Drug abuse	516 (6.5)	558 (7.1)
Psychoses	404 (5.1)	347 (4.4)
Depression	1257 (15.8)	1237 (15.7)

*The Elixhauser Comorbidity Index is a method for measuring patient comorbidity based on the International Classification of Diseases (ICD) diagnosis codes (ICD-9-CM and ICD-10) found in administrative data.[28,29] There were no significant differences in baseline comorbidities between the two study groups except for in uncomplicated diabetes (P=0.03), paralysis (P=0.02), and psychoses (P=0.047).

Table S3. Baseline laboratory values.

		Balanced	Saline
Most recent value in 12 months prior to hospitalization*	**n**	**(n = 7942)**	**(n = 7860)**
Plasma sodium, mmol/L	7677	139 [136-141]	139 [136-141]
Plasma potassium, mmol/L	7675	4.2 [3.8-4.5]	4.1 [3.8-4.5]
Plasma chloride, mmol/L	7675	103 [100-106]	103 [100-106]
Plasma bicarbonate, mmol/L	7675	25 [22-27]	25 [22-27]
Plasma blood urea nitrogen, mg/dL	7677	17 [12-25]	17 [12-25]
Plasma creatinine, mg/dL	7770	0.94 [0.77-1.31]	0.95 [0.76-1.32]
First value between hospitalization and ICU admission†			
Plasma sodium, mmol/L	11562	138 [135-140]	138 [136-141]
Plasma potassium, mmol/L	11558	4.1 [3.7-4.5]	4.1 [3.7-4.5]
Plasma chloride, mmol/L	11547	104 [100-107]	104 [100-108]
Plasma bicarbonate, mmol/L	11505	22 [20-25]	22 [20-25]
Plasma blood urea nitrogen, mg/dL	11547	17 [12-27]	17 [12-27]
Plasma creatinine, mg/dL	11583	1.0 [0.8-1.4]	1.0 [0.8-1.5]
Baseline creatinine‡ – mg/dL	15,802	0.89 [0.74 – 1.10]	0.89 [0.74 – 1.10]
Source of baseline creatinine			
Lowest in 12 months prior to hospitalization§ – no. (%)		3922 (49.4)	3848 (49.0)
Median value – mg/dL		0.83 [0.68 – 1.09]	0.82 [0.67 – 1.10]
Lowest between hospitalization and ICU admission¶ – no. (%)		3157 (39.8)	3186 (40.5)
Median value – mg/dL		0.93 [0.78-1.20]	0.93 [0.78-1.23]
Estimated by three-variable formula‖ – no. (%)		863 (10.9)	826 (10.5)
Median value – mg/dL		0.91 [0.87-0.95]	0.91 [0.87-0.95]

Data are presented as median [25th percentile – 75th percentile]

* Most recent value in 12 months prior to hospitalization is defined as the most recent value in the time period between one year prior to hospital admission and 24 hours prior to hospital admission

† First value between hospitalization and ICU admission is defined as first value in the time period between 24 hours prior to hospital admission and the time of ICU admission.

‡ Baseline creatinine for the study is defined as the lowest plasma creatinine measured in the 12 months prior to hospitalization if available, otherwise the lowest plasma creatinine measured between hospitalization and ICU admission; using the estimated creatinine only for patients without an available plasma creatinine between 12 months prior to hospitalization and the time of ICU admission.

§ Lowest creatinine in the 12 months prior to hospitalization is defined as the lowest available plasma creatinine between 12 months and 24 hours prior to hospital admission.

¶ Lowest creatinine between hospitalization and ICU admission is defined as the lowest available plasma creatinine between 24 hours prior to hospital admission and ICU admission

‖ Baseline creatinine is estimated for patients without a measured value using a previously-described three-variable formula [creatinine (mg/dL) = 0.74 − 0.2 (if female) + 0.08 (if African American) + 0.003 × age (in years)][30]

Table S4. Intravenous isotonic crystalloid in the 24 hours prior to ICU admission.

	Balanced Crystalloid	Saline	
Overall	**(n = 7942)**	**(n = 7860)**	***P* value**
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 125 ± 465	0 [0 – 250]; 400 ± 896	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1200]; 790 ± 1329	0 [0 – 400]; 476 ± 1073	<0.001
Medical ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 212 ± 629	0 [0 – 1000]; 700 ± 1158	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	[0 – 1000]; 676 ± 1250	0 [0 – 0]; 178 ± 632	<0.001
Trauma ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 14 ± 159	0 [0 – 0]; 167 ± 420	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 400]; 381 ± 863	0 [0 – 0]; 184 ± 691	<0.001
Cardiac ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 60 ± 296	0 [0 – 0]; 40 ± 198	0.49
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1500]; 761 ± 1069	456 [0 – 1450]; 807 ± 1038	0.02
Neurological ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 144 ± 427	0 [0 – 500]; 488 ± 1009	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	0 [0 – 1600]; 899 ± 1384	0 [0 – 600]; 463 ± 954	<0.001
Surgical ICU			
0.9% sodium chloride, median [IQR]; mean ± SD, mL	0 [0 – 0]; 149 ± 492	0 [0 – 500]; 428 ± 849	<0.001
Balanced crystalloid, median [IQR]; mean ± SD, mL	1900 [0 – 3200]; 2125 ± 2006	1200 [0 – 2900]; 1724 ± 2074	<0.001

Intravenous isotonic crystalloid in the 24 hours prior to ICU admission includes isotonic crystalloid ordered in the emergency department, operating room, or hospital ward at the study institution, but does not include fluid ordered prior to arrival at the study institution. The isotonic crystalloid ordered in the emergency department was coordinated with the isotonic crystalloid assigned to the three ICUs that admit the majority of patients from the emergency department (medical, trauma, and surgical). Patients in the neurosurgery operating rooms being admitted to the neurological ICU received the isotonic crystalloid assigned to the neurological ICU. Patients in the general surgery and subspecialty surgery operating rooms being admitted to the surgical ICU received the isotonic crystalloid assigned to the surgical ICU. As a result, patients in the balanced crystalloid group received a larger volume of balanced crystalloids in the 24 hours prior to ICU admission than patients in the saline group (P<0.001) and patients in the saline group received a larger volume of 0.9% sodium chloride in the 24 hours prior to ICU admission than patients in the balanced crystalloid group (P<0.001). The isotonic crystalloid ordered in the cardiac surgery operating rooms was not able to be successfully coordinated with the isotonic crystalloid assigned to the cardiac ICU.

Table S5. Volume of intravenous isotonic crystalloid by study group.

	Balanced Crystalloid (n = 7942)	Saline (n = 7860)	*P* value
0.9% sodium chloride, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 0]; 125 ± 465	0 [0 – 250]; 400 ± 896	<0.001
Cumulative volume from ICU admission through day 3	0 [0 – 0]; 374 ± 1300	1000 [0 – 2900]; 1935 ± 2873	<0.001
Cumulative volume from ICU admission through day 7	0 [0 – 0]; 556 ± 1789	1000 [0 – 3231]; 2275 ± 3488	<0.001
Cumulative volume from ICU admission through day 14	0 [0 – 0]; 727 ± 2488	1000 [0 – 3440]; 2468 ± 4080	<0.001
Cumulative volume from ICU admission through day 30	0 [0 – 77]; 832 ± 3003	1020 [0 – 3500]; 2569 ± 4475	<0.001
Cumulative volume from ICU admission through ICU transfer	0 [0 – 0]; 492 ± 2303	1000 [0 – 3000]; 2171 ± 3942	<0.001
Prior to an ICU crossover in fluid assignment	0 [0 – 0]; 323 ± 1571	1000 [0 – 3000]; 2122 ± 3763	<0.001
After an ICU crossover in fluid assignment	0 [0 – 0]; 169 ± 1563	0 [0 – 0]; 49 ± 943	<0.001
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 364 ± 2008	0 [0 – 0]; 420 ± 2036	0.01
Balanced crystalloid, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 1200]; 790 ± 1329	0 [0 – 400]; 476 ± 1073	<0.001
Cumulative volume from ICU admission through day 3	1000 [0 – 2836]; 1872 ± 2744	0 [0 –0]; 142 ± 859	<0.001
Cumulative volume from ICU admission through day 7	1000 [0 – 3000]; 2117 ± 3157	0 [0 – 0]; 238 ± 1244	<0.001
Cumulative volume from ICU admission through day 14	1000 [0 – 3155]; 2237 ± 3446	0 [0 – 0]; 318 ± 1574	<0.001
Cumulative volume from ICU admission through day 30	1000 [0 – 3210]; 2274 ± 3553	0 [0 – 0]; 374 ± 1795	<0.001
Cumulative volume from ICU admission through ICU transfer	1000 [0 – 3000]; 2083 ± 3310	0 [0 – 0]; 216 ± 1394	<0.001
Prior to an ICU crossover in fluid assignment	1000 [0 – 3000]; 2074 ± 3303	0 [0 – 0]; 70 ± 652	<0.001
After an ICU crossover in fluid assignment	0 [0 – 0]; 9 ± 166	0 [0 – 0]; 146 ± 1222	<0.001
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 197 ± 1152	0 [0 – 0]; 167 ± 1163	0.07
Lactated Ringer's, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 0]; 286 ± 837	0 [0 – 0]; 90 ± 434	<0.001
Cumulative volume from ICU admission through day 3	0 [0 – 1000]; 836 ± 2004	0 [0 – 0]; 69 ± 565	<0.001
Cumulative volume from ICU admission through day 7	0 [0 – 1000]; 939 ± 2213	0 [0 – 0]; 106 ± 694	<0.001
Cumulative volume from ICU admission through day 14	0 [0 –1000]; 980 ± 2307	0 [0 – 0]; 139 ± 856	<0.001
Cumulative volume from ICU admission through day 30	0 [0 – 1000]; 997 ± 2355	0 [0 – 0]; 165 ± 991	<0.001
Cumulative volume from ICU admission through ICU transfer	0 [0 – 1000]; 899 ± 2159	0 [0 – 0]; 85 ± 655	<0.001
Prior to an ICU crossover in fluid assignment	0 [0 – 1000]; 896 ± 2154	0 [0 – 0]; 38 ± 417	<0.001
After an ICU crossover in fluid assignment	0 [0 – 0]; 4 ± 92	0 [0 – 0]; 47 ± 486	<0.001
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 100 ± 757	0 [0 – 0]; 86 ± 726	0.04
Plasma-Lyte A®, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 150]; 504 ± 1125	0 [0 – 0]; 386 ± 997	<0.001
Cumulative volume from ICU admission through day 3	0 [0 – 1170]; 1035 ± 2058	0 [0 – 0]; 73 ± 614	<0.001
Cumulative volume from ICU admission through day 7	0 [0 – 1337]; 1178 ± 2437	0 [0 – 0]; 132 ± 993	<0.001
Cumulative volume from ICU admission through day 14	0 [0 – 1433]; 1257 ± 2718	0 [0 – 0]; 180 ± 1257	<0.001
Cumulative volume from ICU admission through day 30	0 [0 – 1455]; 1278 ± 2809	0 [0 – 0]; 208 ± 1417	<0.001
Cumulative volume from ICU admission through ICU transfer	0 [0 – 1250]; 1184 ± 2661	0 [0 – 0]; 131 ± 1205	<0.001
Prior to an ICU crossover in fluid assignment	0 [0 – 1250]; 1179 ± 2656	0 [0 – 0]; 32 ± 502	<0.001
After an ICU crossover in fluid assignment	0 [0 – 0]; 5 ± 123	0 [0 – 0]; 99 ± 1091	<0.001
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 97 ± 828	0 [0 – 0]; 80 ± 785	0.07

Fluid in the 24 hours prior to ICU admission includes fluid ordered in the emergency department, operating room, or hospital ward at the study institution, but does not include fluid ordered prior to arrival to the study institution. Cumulative volume of fluid ordered from ICU admission through days 3, 7, 14, and 30 includes fluid ordered both in the intensive care unit (ICU) and after transfer out of the ICU. Balanced crystalloid includes lactated Ringer's and Plasma-Lyte A®. A total of 6613 patients (83.3%) in the balanced crystalloid group and 6387 patients (81.3%) in the saline group received any volume of isotonic crystalloid between ICU admission and hospital discharge or 30 days. Among all 15,802 patients, the median volume of non-assigned isotonic crystalloid introduced as a result of patients remaining in the ICU from one calendar month to the next was 0 mL [IQR 0 – 0 mL] in both study groups. Only 426 patients (5.4%) in the balanced crystalloid group and 343 patients (4.4%) in the saline group were administered any volume of the non-assigned crystalloid as a result of remaining in the ICU from one calendar month to the next. Among the 1,848 patients in the balanced crystalloid group who remained in the ICU through a change in calendar month or were transferred between ICUs, the total volume of 0.9% sodium chloride introduced as a result of this "crossover" was median 0 mL [IQR 0 – 0 mL] and mean ± SD of 455 ± 1588 mL. Among the 1,863 patients in the saline group who remained in the ICU through a change in calendar month or were transferred between ICUs, the total volume of balanced crystalloid introduced as a result of this "crossover" was median 0 mL [IQR 0 – 0 mL] and mean ± SD of 555 ± 2207 mL. Among the 665 patients in the balanced crystalloid group with a diagnosis of traumatic brain injury, the mean ± SD volume of fluid ordered was 561 ± 2525 mL for 0.09% sodium chloride, 294 ± 1183 mL for lactated Ringer's, and 1407 ± 2657 mL for Plasma-Lyte A®. Among the 698 patients in the saline group with a diagnosis of traumatic brain injury, the mean ± SD volume of fluid ordered was 1670 ± 3149 mL for 0.09% sodium chloride, 51 ± 484 mL for lactated Ringer's, and 154 ± 788 mL for Plasma-Lyte A®.

Table S6. Electronic orders for isotonic crystalloid placed in the ICU.

Study group	Location	Study Months	Orders for assigned crystalloid, No.	Orders for non-assigned crystalloid, No.			Total
				Hyperkalemia	Brain injury	Attending Request	
Balanced	**Overall**	**41**	**12,227**	**348**	**278**	**232**	**13,085**
	Medical	11	4,168	226	15	85	4,494
	Neurological	9	2,541	35	186	65	2,827
	Cardiac	8	2,381	29	4	17	2,431
	Trauma	7	1,515	19	63	29	1,626
	Surgical	6	1,622	39	10	36	1,707
Saline	**Overall**	**41**	**11,991**	--	--	**270**	**12,261**
	Medical	11	3,936	--	--	70	4,006
	Neurological	9	2,373	--	--	82	2,455
	Cardiac	8	2,340	--	--	44	2,384
	Trauma	7	1,589	--	--	29	1,618
	Surgical	6	1,753	--	--	45	1,798
Total		**82**	**24,218**	**348**	**278**	**502**	**25,346**

All orders for intravenous isotonic crystalloid placed through the computerized order entry system in participating intensive care units during the study period are displayed. Overall, 24,218 of 25,346 isotonic crystalloid orders (95.5%) were for the crystalloid assigned to the unit during that month. During months assigned to balanced crystalloid, 12,227 of 13,085 isotonic crystalloid orders (93.4%) were for either lactated Ringer's or Plasma-Lyte A®. During months assigned to saline, 11,991 of 12,261 isotonic crystalloid orders (97.8%) were for 0.9% sodium chloride.

Table S7. Volume of non-study intravenous fluids and blood products by study group.

	Balanced Crystalloid (n = 7942)	Saline (n = 7860)	*P* value
Hypotonic crystalloid, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 0]; 13 ± 136	0 [0 – 0]; 13 ± 115	0.87
Cumulative volume from ICU admission through day 3	0 [0 – 0]; 282 ± 925	0 [0 – 0]; 305 ± 1015	0.23
Cumulative volume from ICU admission through day 7	0 [0 – 0]; 378 ± 1404	0 [0 – 0]; 396 ± 1284	0.47
Cumulative volume from ICU admission through day 14	0 [0 – 0]; 419 ± 1581	0 [0 – 0]; 457 ± 1490	0.69
Cumulative volume from ICU admission through day 30	0 [0 – 0]; 450 ± 1721	0 [0 – 0]; 478 ± 1594	0.63
Cumulative volume from ICU admission through ICU transfer	0 [0 – 0]; 349 ± 1394	0 [0 – 0]; 372 ± 1322	0.10
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 101 ± 884	0 [0 – 0]; 106 ± 801	0.12
Human albumin solutions, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 0]; 44 ± 234	0 [0 – 0]; 37 ± 222	0.07
Cumulative volume from ICU admission through day 3	0 [0 – 0]; 42 ± 219	0 [0 – 0]; 42 ± 219	0.74
Cumulative volume from ICU admission through day 7	0 [0 – 0]; 48 ± 237	0 [0 – 0]; 50 ± 250	0.71
Cumulative volume from ICU admission through day 14	0 [0 – 0]; 52 ± 249	0 [0 – 0]; 56 ± 274	0.84
Cumulative volume from ICU admission through day 30	0 [0 – 0]; 54 ± 259	0 [0 – 0]; 59 ± 292	0.81
Cumulative volume from ICU admission through ICU transfer	0 [0 – 0]; 48 ± 242	0 [0 – 0]; 48 ± 239	0.83
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 6 ± 82	0 [0 – 0]; 11 ± 154	0.58
Blood products, median [IQR]; mean ± SD, mL			
In the 24 hours prior to ICU admission	0 [0 – 0]; 200 ± 1786	0 [0 – 0]; 165 ± 968	>0.99
Cumulative volume from ICU admission through day 3	0 [0 – 0]; 5 ± 91	0 [0 – 0]; 7 ± 144	0.69
Cumulative volume from ICU admission through day 7	0 [0 – 0]; 7 ± 113	0 [0 – 0]; 12 ± 255	>0.99
Cumulative volume from ICU admission through day 14	0 [0 – 0]; 9 ± 137	0 [0 – 0]; 14 ± 270	0.99
Cumulative volume from ICU admission through day 30	0 [0 – 0]; 11 ± 173	0 [0 – 0]; 16 ± 283	0.82
Cumulative volume from ICU admission through ICU transfer	0 [0 – 0]; 10 ± 168	0 [0 – 0]; 14 ± 275	0.76
Cumulative volume from ICU transfer to hospital discharge	0 [0 – 0]; 1 ± 42	0 [0 – 0]; 2 ± 67	0.98

Hypotonic Crystalloid includes 0.45% sodium chloride, 0.225% sodium chloride, and dextrose in water; Human albumin solutions include 20% and 5% albumin; Blood products include packed red blood cells, platelets, and fresh frozen plasma. Only 12 patients received any semisynthetic colloid, including starches, dextrans, or gelatins. The cumulative volume of intravenous medication ordered was median 100 mL [IQR 0 – 446 mL]; 430 ± 1051 mL in the balanced crystalloid group and 100 mL [0 – 400 mL]; 415 mL ± 1064 mL in the saline group (P=0.56). Intravenous medication ordered includes the volume of intermittently administered medications but excludes volume from medication infusions or infusions of intravenous crystalloid given to accompany medication infusions ("piggy-back", "carrier", "chaser", "driver" fluids), which were controlled by study group assignment.

Table S8. Laboratory values.

	Balanced	Saline	
Laboratory value	**(n = 7942)**	**(n = 7860)**	***P* value**
Plasma sodium, mmol/L			
Highest between enrollment and day 30, median [IQR]	140 [138 – 142]	140 [138 – 143]	0.03
Lowest between enrollment and day 30, median [IQR]	136 [133 – 138]	136 [133 – 138]	0.005
> 145 mmol/L between enrollment and day 30, No. (%)	816 (10.3)	886 (11.3)	0.03
< 135 mmol/L between enrollment and day 30, No. (%)	3022 (38.1)	2786 (35.4)	0.002
Plasma potassium, mmol/L			
Highest between enrollment and day 30, median [IQR]	4.5 [4.2 – 5.1]	4.5 [4.1 – 5.1]	0.67
Lowest between enrollment and day 30, median [IQR]	3.6 [3.2 – 3.9]	3.6 [3.2 – 3.9]	0.06
> 5.0 mmol/L between enrollment and day 30, No. (%)	1958 (24.7)	1965 (25.0)	0.51
< 3.0 mmol/L between enrollment and day 30, No. (%)	837 (10.5)	894 (11.4)	0.08
Plasma chloride, mmol/L			
Highest between enrollment and day 30, median [IQR]	108 [105 – 111]	109 [105 – 112]	<0.001
Lowest between enrollment and day 30, median [IQR]	102 [98 – 105]	102 [98 – 106]	<0.001
> 110 mmol/L between enrollment and day 30, No. (%)	1945 (24.5)	2796 (35.6)	<0.001
< 90 mmol/L between enrollment and day 30, No. (%)	306 (3.9)	261 (3.3)	0.08
Plasma bicarbonate, mmol/L			
Highest between enrollment and day 30, median [IQR]	26.0 [24.0 – 29.0]	26.0 [23.0 – 28.3]	<0.001
Lowest between enrollment and day 30, median [IQR]	21.0 [18.0 – 23.0]	20.0 [17.0 – 22.0]	<0.001
> 30 mmol/L between enrollment and day 30, No. (%)	1370 (17.3)	1140 (14.5)	<0.001
< 20 mmol/L between enrollment and day 30, No. (%)	2793 (35.2)	3307 (42.1)	<0.001

Table S9. Multivariable model for Major Adverse Kidney Events within 30 days.

Variable	Odds Ratio	95% CI	*P* value
Study Group (Balanced crystalloids : Saline)	0.90	0.82 – 0.99	0.04
Age, years	1.02	1.01 – 1.02	<0.001
Sex (Male : Female)	1.06	0.96 – 1.17	0.24
Race (Non-White : White)	1.16	1.03 – 1.31	0.01
Source of Admission			
Emergency department (referent)	--	--	--
Operating room	0.25	0.21 – 0.31	<0.001
Transfer from another hospital	1.44	1.25 – 1.65	<0.001
Hospital ward	2.01	1.74 – 2.33	<0.001
Other	0.79	0.62 – 1.02	0.07
Mechanical Ventilation (Yes : No)	2.41	2.17 – 2.68	<0.001
Vasopressor Receipt (Yes : No)	2.45	2.18 – 2.74	<0.001
Sepsis or Septic Shock (Yes : No)	2.50	2.22 – 2.81	<0.001
Traumatic Brain Injury (Yes : No)	2.66	2.11 – 3.35	<0.001

The primary analysis was an intention-to-treat comparison of the primary outcome of Major Adverse Kidney Events within 30 days (MAKE30) between the balanced crystalloid and saline groups using a generalized linear mixed-effects model including fixed effects (group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU). All components of the MAKE30 composite outcome were censored at the time of hospital discharge. Median time from ICU admission to hospital discharge or death was 4.9 days [IQR 2.6 – 8.7 days] in the balanced crystalloid group and 4.9 days [IQR 2.6 – 8.7 days] in the saline group (P=0.77). The effect of study group shown in the table is the conditional effect. The marginal effect was odds ratio, 0.91; 95% confidence interval, 0.84 - 0.99.

Table S10. Sensitivity analyses.

Analysis	n	Odds Ratio	95% CI	*P* Value
Primary analysis (intention-to-treat) Generalized linear mixed-effects model for the primary outcome of MAKE30 with fixed effects (group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU)	15,802	0.90	0.82-0.99	0.04
Modified intention-to-treat The primary analysis was repeated among patients for whom ≥ 500 ml of isotonic crystalloid was ordered in the 72 hours after ICU admission	11,123	0.91	0.81-1.02	0.09
"Washout period" analysis The primary analysis was repeated excluding patients admitted in the 7 days prior to a crossover in ICU crystalloid assignment (simulating a washout period)	12,487	0.91	0.82-1.02	0.11
Excluding patients who experienced crossover or ICU transfer The primary analysis was repeated excluding patients who remained in the ICU through a crossover in crystalloid assignment or who were transferred between study ICUs	12,091	0.93	0.83-1.05	0.25
First ICU admission The primary analysis was repeated including only the first ICU admission in the study for each patient	13,949	0.91	0.82 – 1.01	0.09
Alternative approaches to baseline creatinine				
The primary analysis was repeated among the 14,113 patients (89.3%) with a measured creatinine between 12 months prior to hospital admission and enrollment ('complete cases')	14,113	0.87	0.79 – 0.97	0.01
The primary analysis was repeated using single imputation of baseline creatinine for the 1,689 patients (10.7%) without a measured value between 12 months prior to hospital admission and enrollment	15,802	0.89	0.80 – 0.99	0.03
The primary analysis was repeated using single imputation of baseline creatinine for the 8,032 patients (50.8%) without a measured value between 12 months prior to hospital admission and 24 hours prior to hospital admission	15,802	0.89	0.80 – 0.99	0.03
The primary analysis was repeated using the first creatinine after enrollment as baseline for the 1,689 patients (10.7%) without a measured value between 12 months prior to hospital admission and enrollment	15,802	0.90	0.81 – 0.99	0.04
The primary analysis was repeated using the highest creatinine between enrollment and 30 days as baseline for the 1,689 patients (10.7%) without a measured value between 12 months prior to hospital admission and enrollment	15,802	0.89	0.80 – 0.99	0.03
The primary analysis was repeated using the lowest creatinine between enrollment and 30 days as baseline for the 1,689 patients (10.7%) without a measured value between 12 months prior to hospital admission and enrollment	15,802	0.91	0.82 – 1.00	0.05
Alternative approaches to multivariable modeling				
Generalized linear mixed-effects model used for the primary intention-to-treat analysis (as above) with the additional covariate of predicted in-hospital mortality as a fixed effect	15,802	0.88	0.79-0.98	0.02
Generalized linear mixed-effects model for the primary outcome of MAKE30 with group assignment and time from	15,802	0.91	0.83-0.99	0.04

beginning enrollment as fixed effects and ICU as a random effect (accounting for intra-cluster correlation and change in the background rate of MAKE30 over time)				
Generalized linear mixed-effects model for the primary outcome of MAKE30 with group assignment as a fixed effect and time from beginning enrollment and ICU as random effects (accounting for intra-cluster correlation and allowing the change in the background rate of MAKE30 to differ between clusters)	15,802	0.91	0.84-0.99	0.049
Generalized linear mixed-effects model for the primary outcome of MAKE30 with group assignment as a fixed effect and time from beginning enrollment and the interaction between ICU and study period as random effects (accounting for intra-cluster correlation, intra-period correlation, intra-cluster intra-period correlation, and allowing the change in the background rate of MAKE30 to differ between clusters)	15,802	0.91	0.84-1.02	0.05
Generalized linear mixed-effects model for the primary outcome of MAKE30 with group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressors, sepsis, and traumatic brain injury as a fixed effects and time from beginning enrollment and the interaction between ICU and study period as random effects (accounting for intra-cluster correlation, intra-period correlation, intra-cluster intra-period correlation, pre-specified baseline covariates, and allowing the change in the background rate of MAKE30 to differ between clusters)	15,802	0.91	0.84-1.02	0.05
Generalized linear mixed-effects model for the outcome of "30-day in-hospital mortality or new RRT" with fixed effects (group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury) and random effects (ICU)	15,802	0.89	0.80-0.99	0.04
Generalized linear mixed-effects model for the outcome of 30-day in-hospital mortality with fixed effects (group assignment, and predicted risk of in-hospital mortality) and random effects (ICU)	15,802	0.87	0.77-0.99	0.03
Logistic regression model for the outcome of 30-day in-hospital mortality with covariates of group assignment, predicted risk of in-hospital mortality, and ICU	15,802	0.87	0.77-0.99	0.03
Generalized estimating equations for the primary outcome of MAKE30 with covariates of group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury and an exchangeable correlation structure with ICU (odds ratio represents marginal effect).	15,802	0.91	0.82-1.00	0.048
Multivariate Cox proportional-hazards model for survival analysis of the three components of the MAKE30 outcome with censoring at hospital discharge, fixed effects of group assignment, age, sex, race, source of admission, mechanical ventilation, vasopressor receipt, diagnosis of sepsis, and diagnosis of traumatic brain injury, and a random effect (the frailty) of ICU.	15,802	Hazard Ratio 0.92	0.85-0.99	0.04

Odds of experiencing a Major Adverse Kidney Event within 30 days (MAKE30) are presented for patients assigned to the balanced crystalloid group compared with patients assigned to the saline group. With regard to the sensitivity

analysis including only each patient's first ICU admission during the study period, there were 12,596 patients with only one qualifying ICU admission during the study period, 1,057 with two, 198 with three, 54 with four, and 44 with five or more; for a total of 15,802 ICU admissions among 13,949 unique patients. Multiple alternative approaches to assigning baseline creatinine for those without measured values are presented. Single imputation of missing baseline creatinine utilized the following variables: age, gender, race, group assignment, source of admission, primary diagnosis, mechanical ventilation, vasopressor receipt, receipt of renal replacement therapy prior to enrollment, total volume of isotonic crystalloid ordered in the first 30 days, predicted-in-hospital mortality, observed in-hospital 30-day mortality, new receipt of renal replacement therapy, minimum plasma creatinine between enrollment and 30 days, maximum plasma creatinine between enrollment and 30 days, and final plasma creatinine between enrollment and 30 days. All sensitivity analyses were pre-specified except the alternative approaches to multivariable modeling which were *post-hoc*.[1]

Table S11. Indications for new renal replacement therapy.

	Balanced	Saline	
Indications for new RRT among patients who received new RRT, No. (%)	**(n = 189)**	**(n = 220)**	***P* value**
Oliguria	144 (76.2)	180 (81.8)	0.16
Hyperkalemia with plasma potassium > 6.5 mEq/L	21 (11.1)	27 (12.3)	0.72
Acidemia with pH < 7.20	56 (29.6)	64 (29.1)	0.91
Blood urea nitrogen > 70 mg/dL	82 (43.4)	106 (48.2)	0.33
Plasma creatinine > 3.39 mg/dL	111 (58.7)	135 (61.4)	0.59
Organ edema	58 (30.7)	66 (30.0)	0.88
Other renal failure–related indication	19 (10.1)	21 (9.5)	0.86
Other non–renal failure–related indication	42 (22.2)	54 (24.5)	0.58

The decision to initiate renal replacement therapy was made by treating clinicians. Potential indications for renal replacement therapy (RRT) present at the time of RRT initiation were identified via manual chart review by study personnel blinded to group assignment. Patients could have more than one indication for RRT present. Oliguria was defined as urine output less than 5 ml/kg/hour for at least 6 hours.[10] Organ edema was considered present if the clinical team or radiology reports documented the presence of cerebral edema or pulmonary edema. Other non-renal failure-related indications for renal replacement therapy included tumor lysis syndrome, rhabdomyolysis, acute liver failure with cerebral edema, drug or toxic alcohol ingestion, iodinated contrast or gadolinium receipt, sickle cell crisis, post-operative right ventricular systolic failure, and acidemia during receipt of extra-corporeal membrane oxygenation. In a *post-hoc* comparison, there was no difference between the balanced crystalloid and saline groups in the lowest plasma bicarbonate concentration on the day new RRT was initiated (median 18.0 mmol/L [IQR 15.0-21.0 mmol/L] vs median 18.0 mmol/L [IQR 15.0-21.0 mmol/L]; P=0.93). The median duration of in-hospital RRT was 3.0 days [IQR 1.0-10.0 days] in the balanced crystalloid group and 4.0 days [IQR 1.0-8.0 days] in the saline group (P=0.54). A total of 37 of 7458 patients (0.5%) in the saline group who had not received RRT prior to ICU admission continued to receive new RRT after hospital discharge compared with 35 of 7558 patients (0.5%) in the balanced crystalloid group (P=0.77)

Table S12. Highest stage of acute kidney injury developing after enrollment.

	Balanced (n=7558)	Saline (n=7458)	*P* value
Highest stage of incident AKI by KDIGO criteria, No (%)			0.15
None	6313 (83.5)	6166 (82.7)	
Stage I	438 (5.8)	434 (5.8)	
Stage II	299 (4.0)	330 (4.4)	
Stage III	508 (6.7)	528 (7.1)	

In this *post-hoc* analysis, the highest stage of acute kidney injury (AKI) developing between enrollment and the first of hospital discharge or 30 days is compared between study groups. Incident AKI is defined using Kidney Disease Improving Global Outcomes (KDIGO) creatinine criteria[10] as follows:

- Stage I AKI is defined as a plasma creatinine value that is increased ≥ 0.3 mg/dL from a prior post-enrollment value and either 1.5-1.9 times greater than baseline or 1.5-1.9 times greater than the lowest prior on-study value;
- Stage II AKI is defined as a creatinine value that is increased ≥ 0.3 mg/dL from a prior post-enrollment value and either 2.0-2.9 times greater than baseline or 2.0-2.9 times greater than the lowest prior post-enrollment value; and
- Stage III AKI is defined as receipt of new RRT or a creatinine value that is increased ≥ 0.3 mg/dL from a prior post-enrollment value and either ≥ 3.0 times greater than baseline, ≥ 3.0 times greater than the lowest prior post-enrollment value, or ≥ 4.0 mg/dL.

SUPPLEMENTAL FIGURES

Figure S1. Study group assignment during the trial.

The five participating intensive care units (clusters) were randomized to a sequence of alternating crystalloid group assignments (saline during even-numbered months and balanced crystalloid during odd-numbered months, or vice versa). Each intensive care unit spent an equal number of months assigned to balanced crystalloids (B) and saline (S).

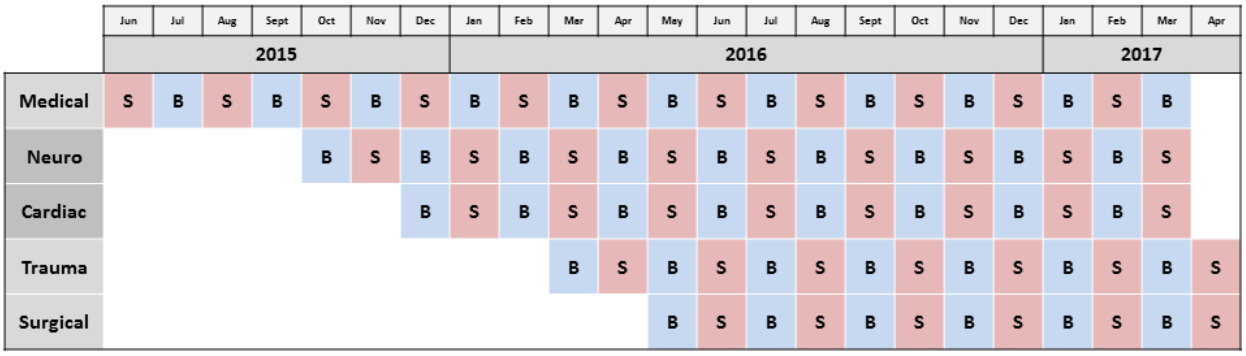


Figure S2. Flow of participants through the trial.

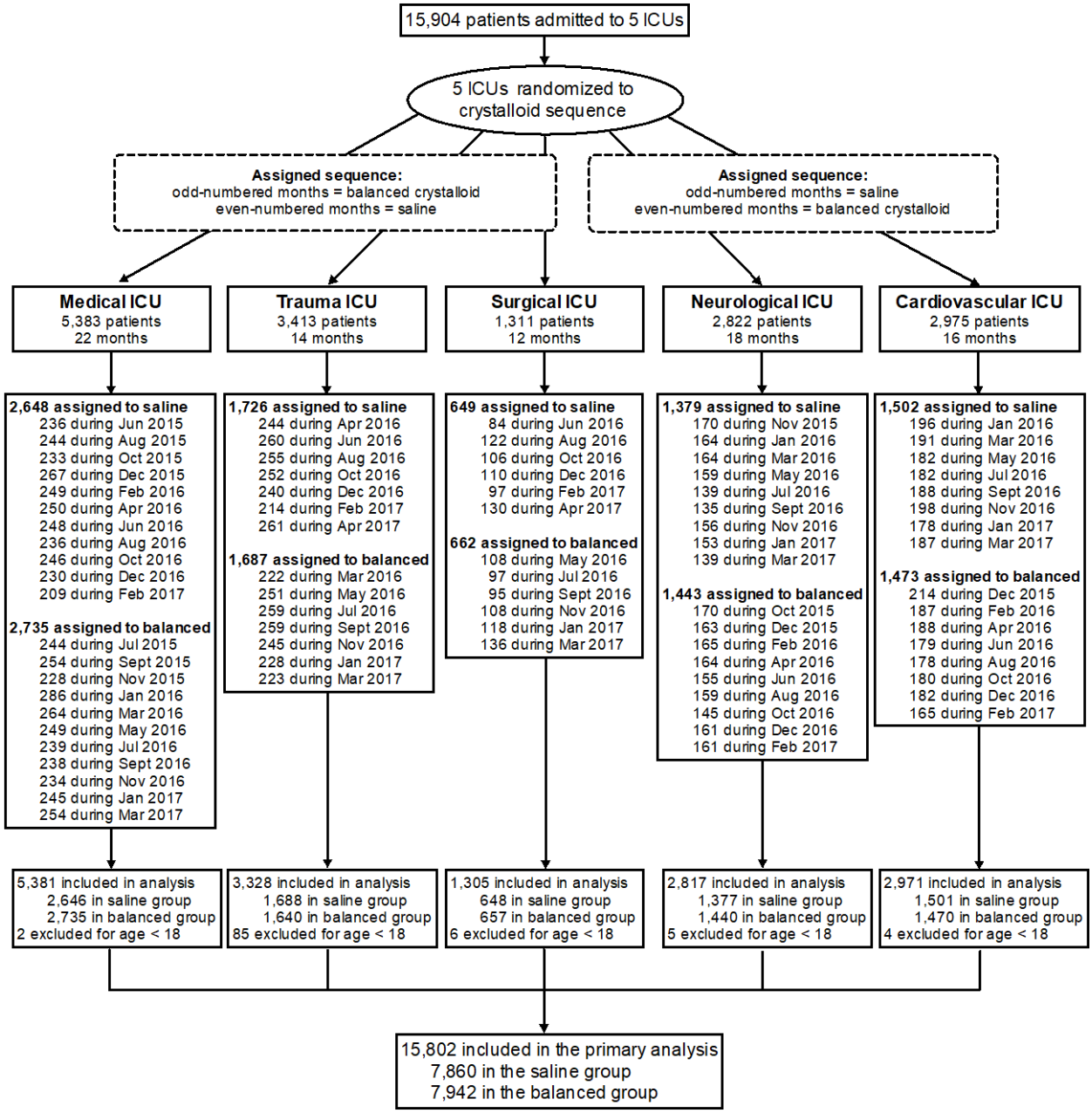


Figure S3. Laboratory Values by Study Arm.
The mean and 95% confidence interval for the first measurement of each laboratory value each day are displayed for patients in the balanced crystalloid (blue) and saline (red) groups using locally weighted scatterplot smoothing. Plasma laboratory values at hospital presentation were similar between groups (Table S3), but, because fluid therapy in the emergency department and operating room was coordinated with the ICU to which patients were being admitted, values for plasma sodium and chloride differed between the balanced crystalloid and saline groups at ICU admission.

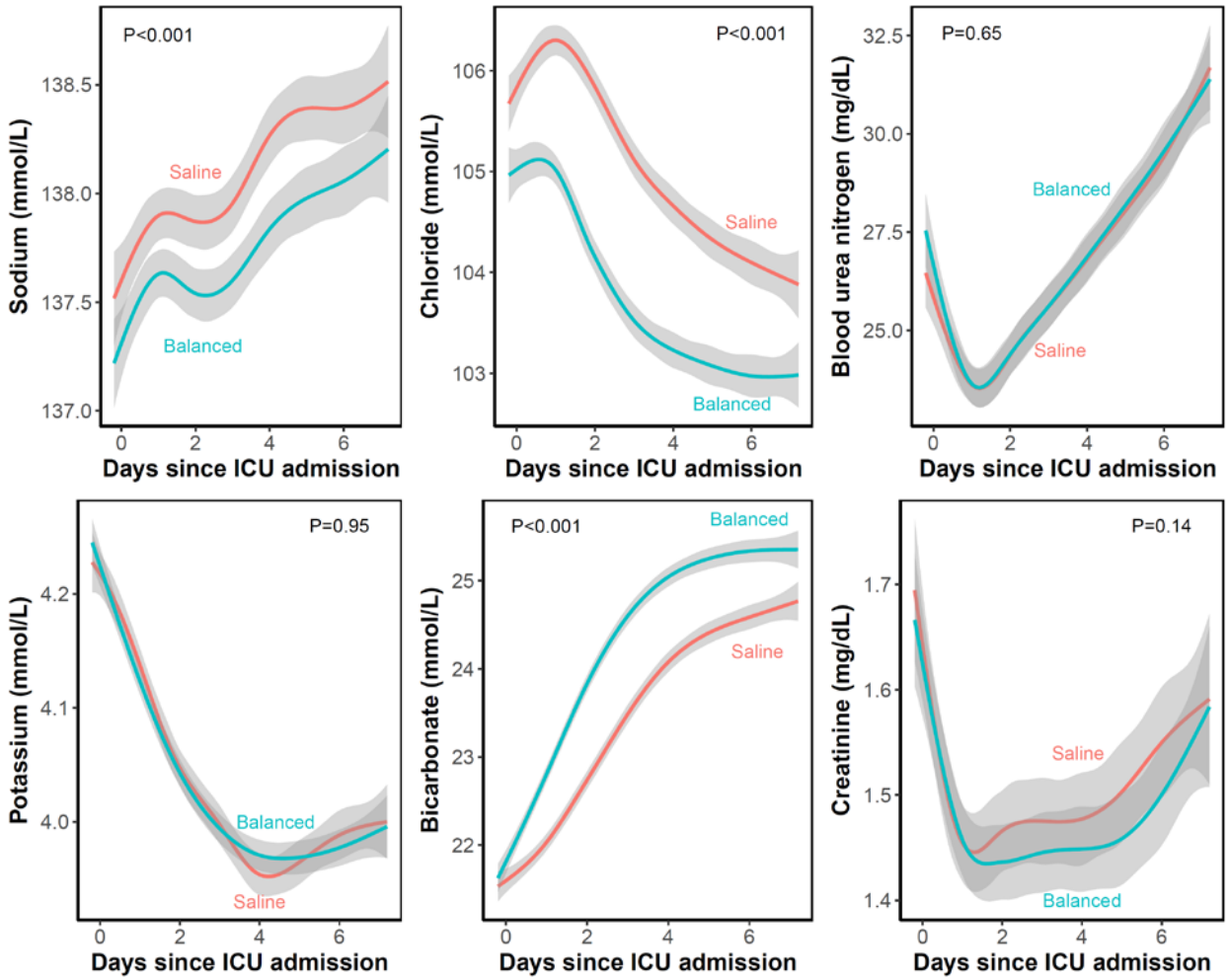


Figure S4. Plasma chloride concentration relative to volume of crystalloid.
The highest plasma chloride concentration between enrollment and day 30 is compared between patients assigned to the balanced crystalloid (blue) and saline (red) groups relative to the total volume of isotonic crystalloid ordered between enrollment and the first of hospital discharge or 30 days. The difference in highest plasma chloride concentration between the balanced crystalloid and saline groups was larger for patients for whom larger volumes of isotonic crystalloid were ordered (P value for interaction <0.001). Colored vertical bars display a histogram of the proportion of patients in each group for whom a given volume of crystalloid was ordered. Even patients for whom no isotonic crystalloid was ordered after ICU admission may have received the assigned crystalloid in the emergency department or operating room prior to ICU admission.

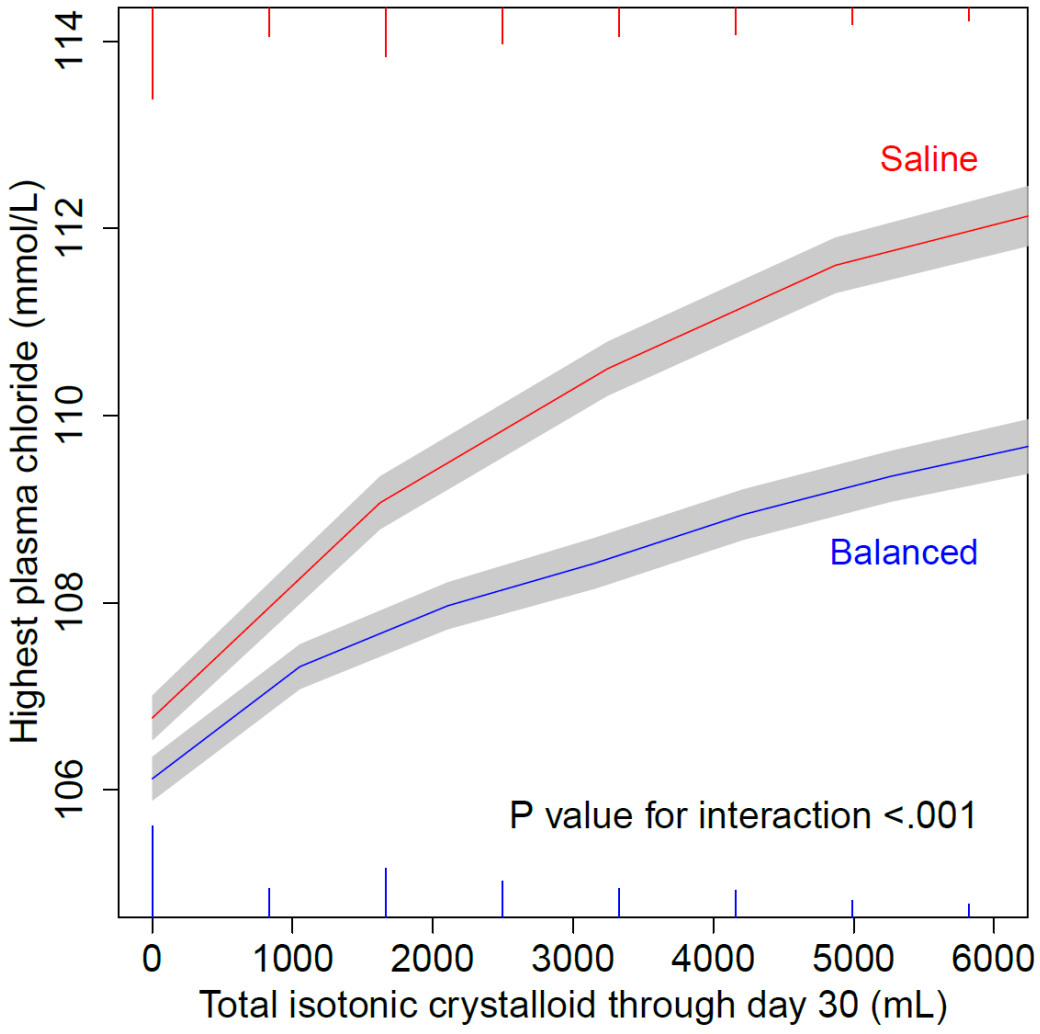


Figure S5. Plasma bicarbonate concentration relative to volume of crystalloid.
The lowest plasma bicarbonate concentration between enrollment and day 30 is compared between patients assigned to the balanced crystalloid (blue) and saline (red) groups relative to the total volume of isotonic crystalloid ordered between enrollment and the first of hospital discharge or 30 days. The difference in lowest plasma bicarbonate concentration between the balanced crystalloid and saline groups was larger for patients for whom larger volumes of isotonic crystalloid were ordered (P value for interaction <0.001). Colored vertical bars display a histogram of the proportion of patients in each group for whom a given volume of crystalloid was ordered. Even patients for whom no isotonic crystalloid was ordered after ICU admission may have received the assigned crystalloid in the emergency department or operating room prior to ICU admission.

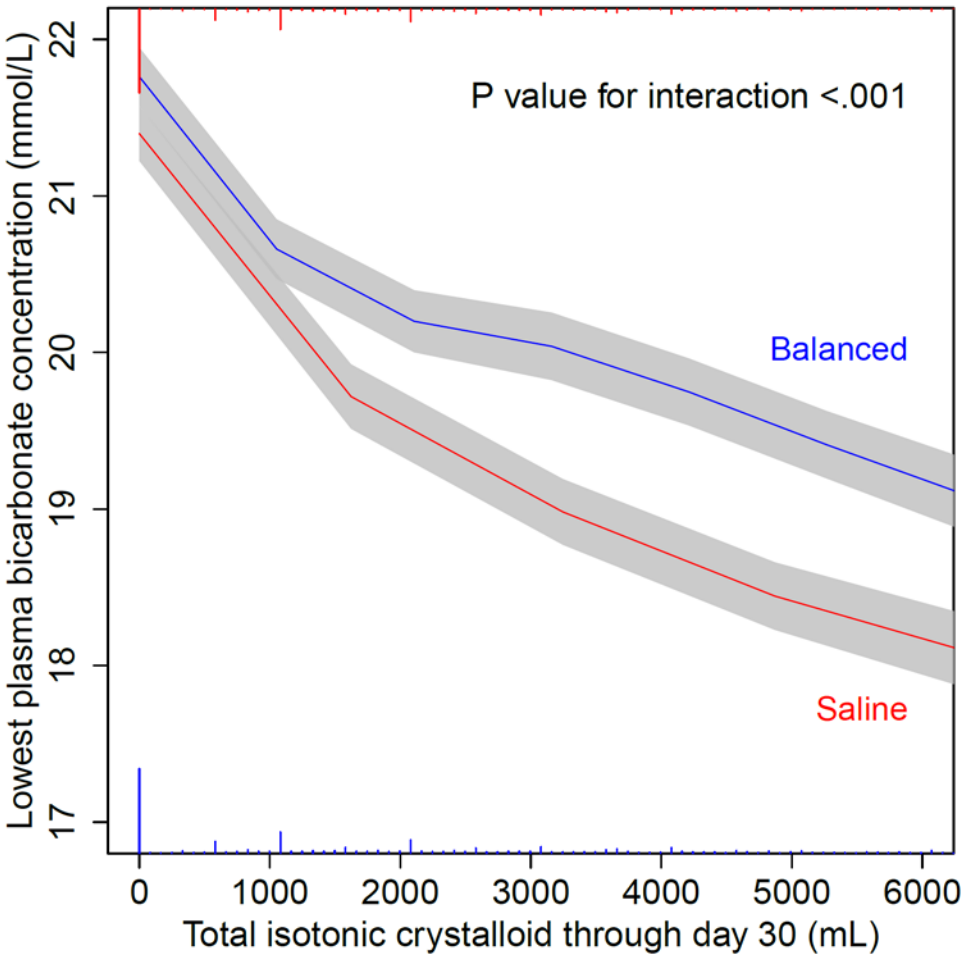


Figure S6. Components of the MAKE30 composite outcome.
For the balanced crystalloid (left) and saline (right) groups, the percentages of patients who experienced in-hospital mortality, new RRT (among survivors), and persistent renal dysfunction (among survivors without new RRT) are displayed. The overall incidence of the Major Adverse Kidney Events within 30 days (MAKE30) composite outcome was 14.3% in the balanced crystalloid group and 15.4% in the saline group. P value is for the intention-to-treat comparison of the balanced crystalloid and saline groups using a pre-specified generalized linear mixed-effects model with ICU as a random effect and pre-specified co-variates as fixed effects.

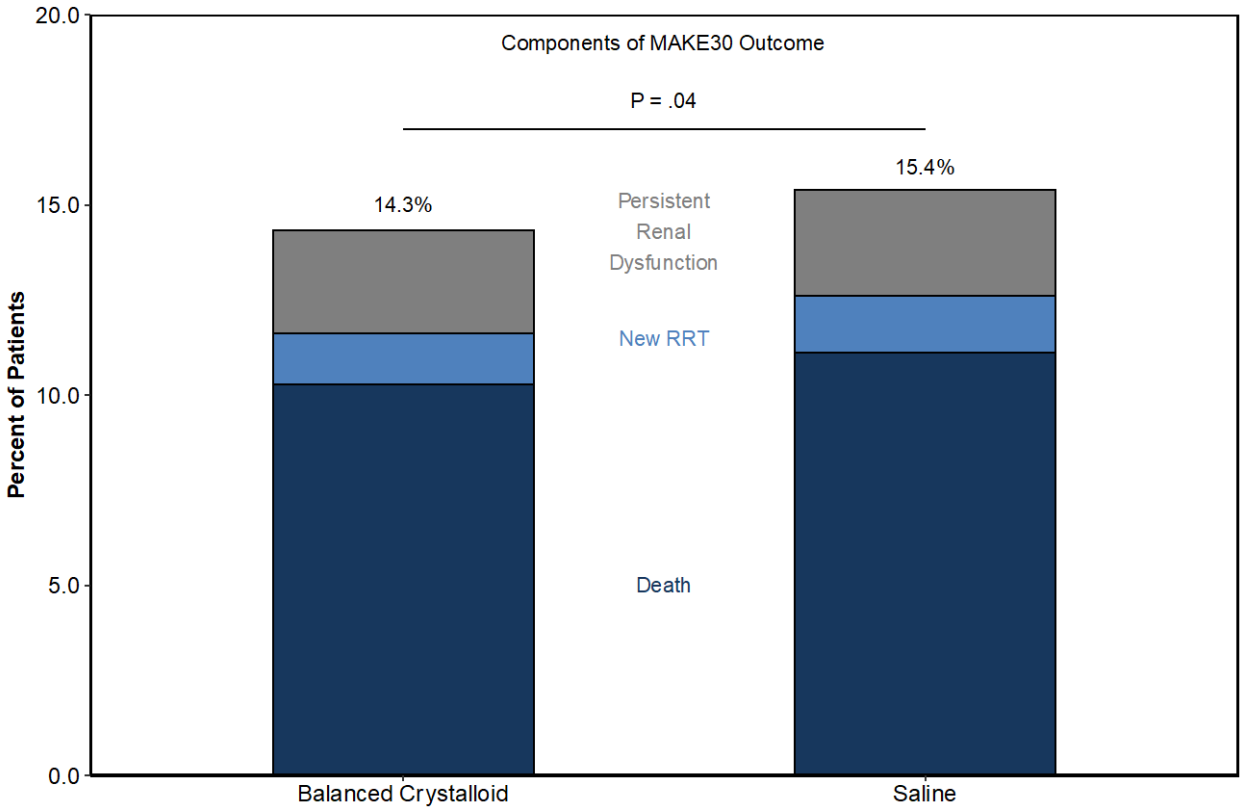
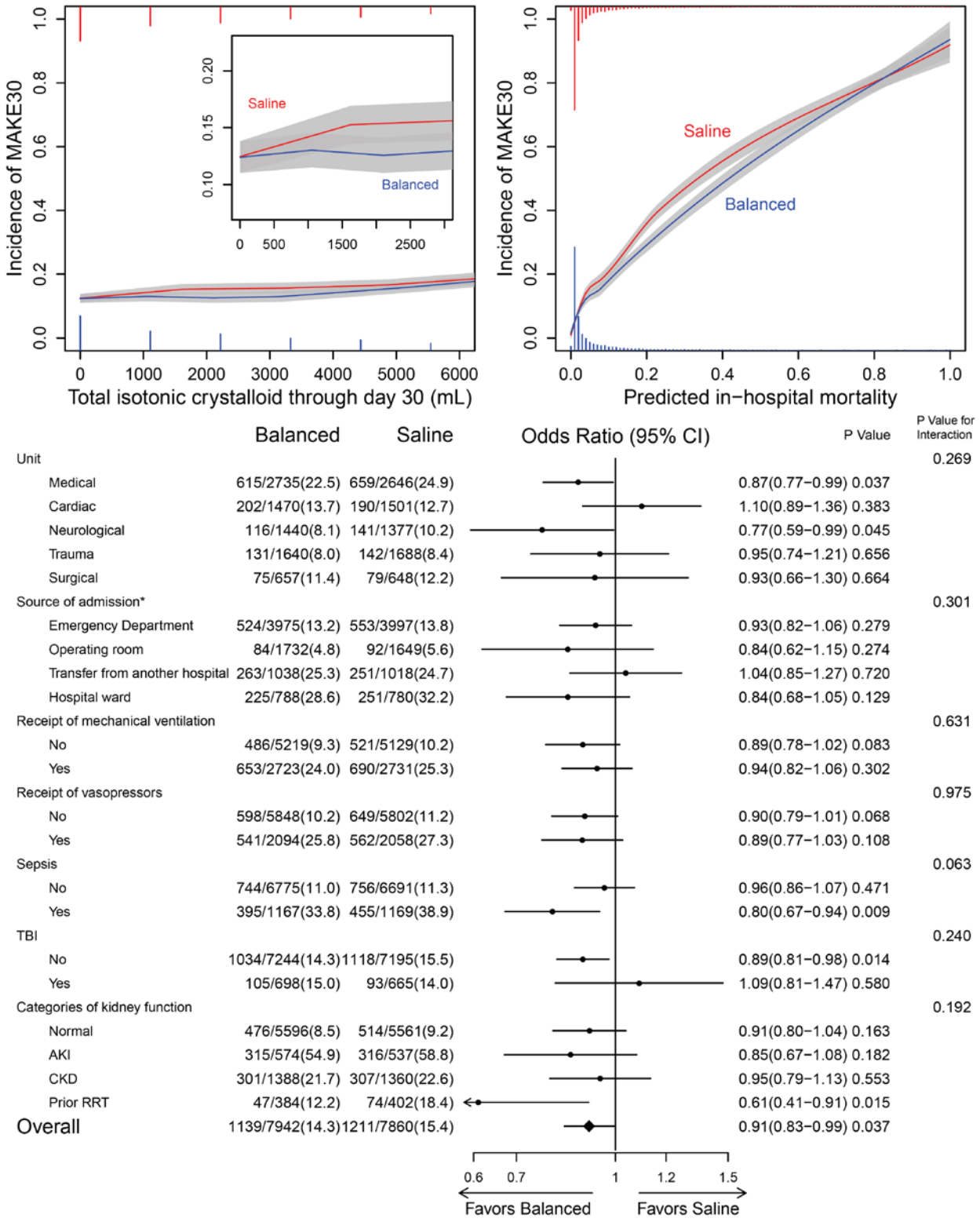
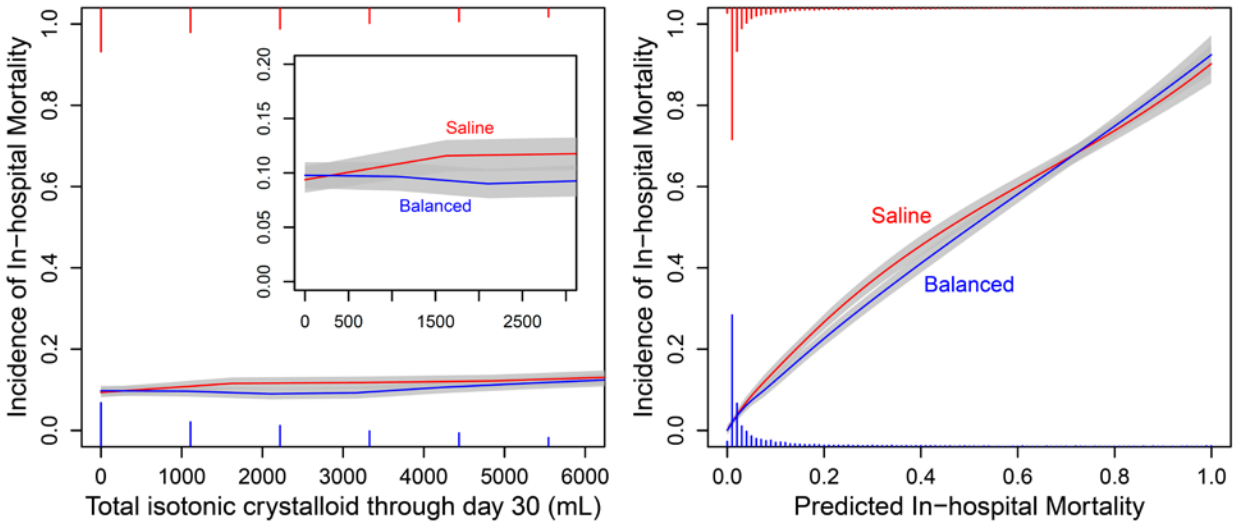


Figure S7. Heterogeneity of treatment effect for MAKE30.



The upper left panel displays the primary outcome of Major Adverse Kidney Events within 30 days (MAKE30) for patients in the balanced crystalloid and saline groups relative to the total volume of isotonic crystalloid in the 30 days after ICU admission. The upper right panel displays the incidence of MAKE30 relative to patients' baseline risk of in-hospital mortality as estimated by Vizient™ (formerly University HealthSystem Consortium[24]). Colored vertical bars represent a histogram of the proportion of patients in each group with a given volume of isotonic crystalloid (upper left panel) or with a given baseline risk of in-hospital mortality (upper right panel). For each pre-specified subgroup, the lower panel displays the number and percentage of patients in each study group who experienced MAKE30, the odds ratio and 95% confidence interval for experiencing MAKE30 in the balanced crystalloid group compared with the saline group, and the P values within the subgroup and for the test of interaction derived from a generalized linear mixed-effects model adjusting only for ICU as a random effect (analyses adjusting for additional covariates are displayed in Table 2 and Tables S9-10 in the Supplementary Appendix). Normal kidney function at enrollment is defined as the absence of acute kidney injury, chronic kidney disease (CKD), or renal replacement therapy prior to enrollment. Acute kidney injury refers to patients without CKD whose first creatinine after enrollment was at least 200% of the baseline value OR both (1) greater than 4.0 mg/dL and (2) increased at least 0.3 mg/dL from the baseline value.[10] CKD refers to patents with a glomerular filtration rate less than 60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation using the patient's baseline creatinine value.[11] Prior renal replacement therapy refers to patients known to have received any form of renal replacement therapy prior to enrollment.
*Additional sources of admission include outpatient (n=722) and transfer from another ICU within the hospital (n=103).

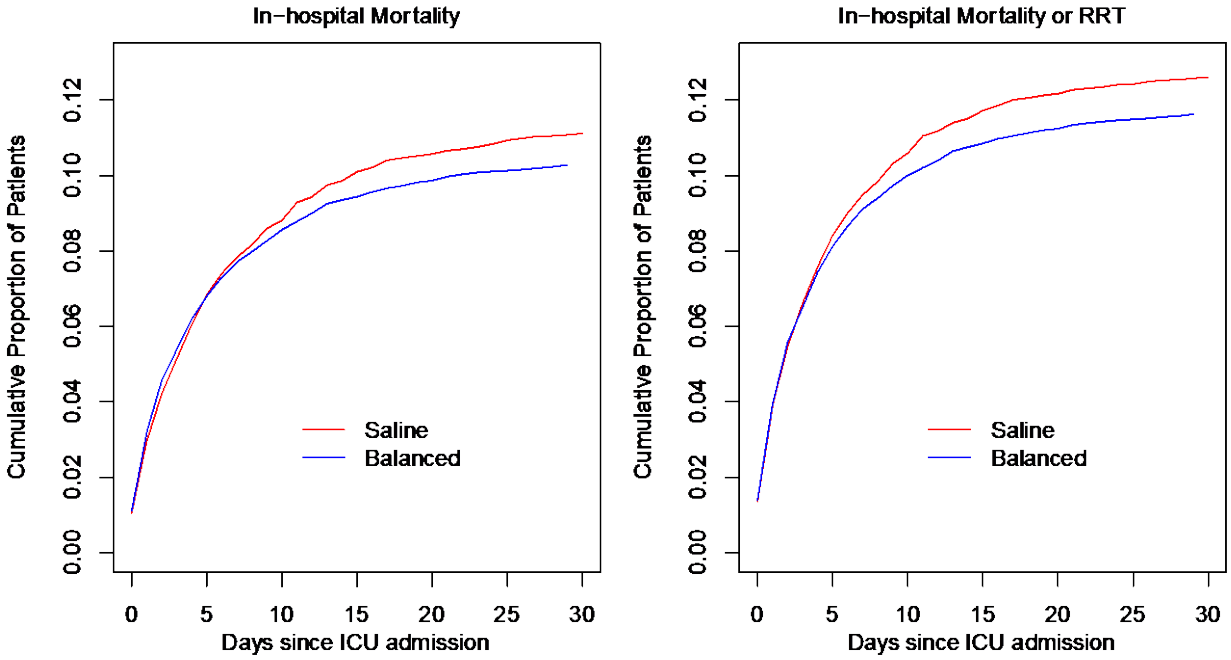
Figure S8. Heterogeneity of treatment effect for 30-day in-hospital mortality.



	Balanced	Saline	Odds Ratio (95% CI)	P Value	P Value for Interaction
Unit					0.201
Medical	418/2735(15.3)	467/2646(17.6)		0.84(0.73−0.97)	0.019
Cardiac	124/1470(8.4)	108/1501(7.2)		1.19(0.91−1.55)	0.208
Neurological	109/1440(7.6)	126/1377(9.2)		0.81(0.62−1.06)	0.130
Trauma	125/1640(7.6)	131/1688(7.8)		0.98(0.76−1.27)	0.881
Surgical	42/657(6.4)	43/648(6.6)		0.96(0.62−1.49)	0.859
Source of admission*					0.562
Emergency Department	402/3975(10.1)	441/3997(11.0)		0.90(0.78−1.04)	0.155
Operating room	41/1732(2.4)	46/1649(2.8)		0.81(0.53−1.24)	0.338
Transfer from another hospital	190/1038(18.3)	175/1018(17.2)		1.08(0.86−1.36)	0.500
Hospital ward	156/788(19.8)	178/780(22.8)		0.83(0.65−1.07)	0.150
Receipt of mechanical ventilation					0.233
No	302/5219(5.8)	341/5129(6.6)		0.85(0.72−0.99)	0.043
Yes	516/2723(18.9)	534/2731(19.6)		0.97(0.84−1.11)	0.656
Receipt of vasopressors					0.790
No	394/5848(6.7)	437/5802(7.5)		0.88(0.76−1.01)	0.077
Yes	424/2094(20.2)	438/2058(21.3)		0.90(0.77−1.05)	0.190
Sepsis					0.096
No	524/6775(7.7)	531/6691(7.9)		0.97(0.85−1.10)	0.601
Yes	294/1167(25.2)	344/1169(29.4)		0.80(0.67−0.97)	0.020
TBI					0.166
No	713/7244(9.8)	784/7195(10.9)		0.88(0.79−0.98)	0.019
Yes	105/698(15.0)	91/665(13.7)		1.12(0.82−1.51)	0.475
Categories of kidney function					0.193
Normal	389/5596(7.0)	418/5561(7.5)		0.92(0.79−1.06)	0.231
AKI	156/574(27.2)	144/537(26.8)		1.02(0.78−1.33)	0.892
CKD	226/1388(16.3)	239/1360(17.6)		0.91(0.75−1.12)	0.377
Prior RRT	47/384(12.2)	74/402(18.4)		0.61(0.41−0.91)	0.015
Overall	818/7942(10.3)	875/7860(11.1)		0.91(0.82−1.01)	0.064

The upper left panel displays the secondary outcome of 30-day in-hospital mortality for patients in the balanced crystalloid and saline groups relative to the total volume of isotonic crystalloid ordered in the 30 days after ICU admission. The upper right panel displays 30-day in-hospital mortality relative to patients' baseline risk of in-hospital mortality as estimated by Vizient™ (formerly University HealthSystem Consortium).[23] Colored vertical bars display a histogram of the proportion of patients in each group for whom a given volume of isotonic crystalloid was ordered (upper left panel) or with a given baseline risk of in-hospital mortality (upper right panel). The mean (SD) and median [IQR] expected in-hospital mortality were 9.44% ± 18.76% and 1.53% [IQR 0.40% - 7.91%], respectively, in the balanced crystalloid group versus 9.57% ± 18.96% and 1.55% [IQR 0.44%- 8.02%], respectively, in the saline group. For each pre-specified subgroup, the lower panel displays the unadjusted number and percentage of patients in each study group who experienced 30-day in-hospital mortality, the odds ratio with 95% confidence interval (CI) for experiencing 30-day in-hospital mortality in the balanced group compared with the saline group, and the P values within the subgroup and for the test of interaction derived from a pre-specified generalized linear mixed-effects model adjusting only for ICU as a random effect. Normal kidney function at enrollment is defined as the absence of acute kidney injury (AKI), chronic kidney disease (CKD), or renal replacement therapy (RRT) prior to enrollment. AKI refers to patients without CKD whose first creatinine after enrollment was at least 200% of the baseline value OR both (1) greater than 4.0 mg/dL and (2) increased at least 0.3 mg/dL from the baseline value.[10] CKD refers to patents with a glomerular filtration rate less than 60 ml/min per 1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation using the patient's baseline creatinine value.[11] Prior RRT refers to patients known to have received any form of RRT prior to enrollment.
*Additional sources of admission include outpatient (n=722) and transfer from another ICU within the hospital (n=103).

Figure S9. Cumulative proportion of patients experiencing death or RRT.
The cumulative proportion of patients in each study group with in-hospital mortality (left panel) or in-hospital mortality or new renal replacement therapy (RRT) (right panel) is displayed for each study group between ICU admission and 30 days after ICU admission. The denominator at all time-points is 7942 patients in the balanced crystalloid group and 7860 patients in the saline group. In Cox proportional-hazards modeling adjusting for the pre-specified covariates included in the primary analysis with a random effect (frailty term) for ICU, the hazard ratio with balanced crystalloids compared to saline was 0.93 (95% CI 0.84-1.02; P=0.11) for death and 0.91 (95% CI 0.83-0.99; P=0.03) for death or new RRT.



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